

## Addendum

1. CELL ADHESION-INHIBITING ANTIINFLAMMATORY AND IMMUNE-SUPPRESSIVE COMPOUNDS

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**CELL ADHESION-INHIBITING ANTIINFLAMMATORY**  
**AND IMMUNE-SUPPRESSIVE COMPOUNDS**

This application is a continuation-in-part of Application Serial Number 09/474,517, filed December 29, 1999, which is a continuation-in-part of provisional Application Serial Number 60/114,097, filed December 29, 1998.

**Technical Field**

The present invention relates to compounds that are useful for treating inflammatory and immune diseases, to pharmaceutical compositions comprising these compounds, and to methods of inhibiting inflammation or suppressing immune response in a mammal.

**Background**

Inflammation results from a cascade of events that includes vasodilation accompanied by increased vascular permeability and exudation of fluid and plasma proteins. This disruption of vascular integrity precedes or coincides with an infiltration of inflammatory cells. Inflammatory mediators generated at the site of the initial lesion serve to recruit inflammatory cells to the site of injury. These mediators

(chemokines such as IL-8, MCP-1, MIP-1, and RANTES, complement fragments and lipid mediators) have chemotactic activity for leukocytes and attract the inflammatory cells to the inflamed lesion. These chemotactic mediators which cause circulating leukocytes to localize at the site of inflammation require the cells to cross the vascular endothelium at a precise location. This leukocyte recruitment is accomplished by a process called cell adhesion.

Cell adhesion occurs through a coordinately regulated series of steps that allow the leukocytes to first adhere to a specific region of the vascular endothelium and then cross the endothelial barrier to migrate to the inflamed tissue (Springer, T.A., 1994, Traffic Signals for Lymphocyte Recirculation and Leukocyte Emigration: The Multistep Paradigm, Cell 76: 301-314; Lawrence, M. B., and Springer, T. A., 1991, Leukocytes' Roll on a Selectin at Physiologic Flow Rates: Distinction from and Prerequisite for Adhesion Through Integrins, Cell.65: 859-873; von Adrian, U., Chambers, J. D., McEnvoy, L.M., Bargatze, R.F., Arfos, K.E, and Butcher, E.C., 1991, Two-Step Model of Leukocyte-Endothelial Cell Interactions in Inflammation, Proc. Natl. Acad. Sci. USA 88: 7538-7542; and Ley, K., Gaehtgens, P., Fennie, C., Singer, M.S., Lasky, L.H. and Rosen, S.D.,1991, Lectin-Like Cell Adhesion Molecule 1 Mediates Rolling in Mesenteric Venules *in vivo*, Blood 77: 2553-2555). These steps are mediated by families of adhesion molecules such as integrins, Ig supergene family members, and selectins which are expressed on the surface of the circulating leukocytes and on the vascular endothelial cells. The first step consists of leukocytes rolling along the vascular endothelial cell lining in the region of inflammation. The

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rolling step is mediated by an interaction between a leukocyte surface oligosaccharide, such as Sialylated Lewis-X antigen (SLe<sup>x</sup>), and a selectin molecule expressed on the surface of the endothelial cell in the region of inflammation. The selectin molecule is not normally expressed on the surface of endothelial cells but rather is induced by the action of inflammatory mediators such as TNF- $\alpha$  and interleukin-1. Rolling decreases the velocity of the circulating leukocyte in the region of inflammation and allows the cells to more firmly adhere to the endothelial cell. The firm adhesion is accomplished by the interaction of integrin molecules that are present on the surface of the rolling leukocytes and their counter-receptors (the Ig superfamily molecules) on the surface of the endothelial cell. The Ig superfamily molecules or CAMs (Cell Adhesion Molecules) are either not expressed or are expressed at low levels on normal vascular endothelial cells. The CAM's, like the selectins, are induced by the action of inflammatory mediators like TNF-alpha and IL-1. The final event in the adhesion process is the extravasation of leukocytes through the endothelial cell barrier and their migration along a chemotactic gradient to the site of inflammation. This transmigration is mediated by the conversion of the leukocyte integrin from a low avidity state to a high avidity state. The adhesion process relies on the induced expression of selectins and CAM's on the surface of vascular endothelial cells to mediate the rolling and firm adhesion of leukocytes to the vascular endothelium.

The interaction of the intercellular adhesion molecule ICAM-1 (cd54) on endothelial cells with the integrin LFA-1 on leukocytes plays an important role in endothelial-leukocyte contact. Leukocytes bearing high-affinity LFA-1 adhere to

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5 have numerous abnormalities in their inflammatory responses.

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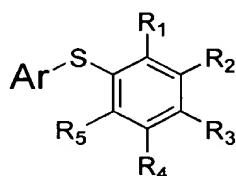
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### Summary of The Invention

The present invention provides compounds of formula I, below,



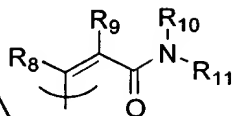
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or a pharmaceutically-acceptable salt or prodrug thereof,

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are independently selected from

- a. hydrogen,
- b. halogen,
- c. alkyl,
- d. haloalkyl,
- e. alkoxy,
- f. cyano,
- g. nitro,
- h. carboxaldehyde, and

with the proviso that at least one of R<sub>1</sub> or R<sub>3</sub> is a "cis-cinnamide" or a "trans-cinnamide", defined as



"cis-cinnamide"



"trans-cinnamide",

wherein R<sub>8</sub> and R<sub>9</sub> are independently selected from

- a. hydrogen, and
- b. alkyl,
- c. carboxy alkyl,
- d. alkylaminocarbonyl alkyl, and
- e. dialkylaminocarbonyl alkyl,

and R<sub>10</sub> and R<sub>11</sub> are independently selected from

- a. hydrogen,
- b. alkyl,
- c. cycloalkyl,
- d. alkoxycarbonylalkyl,
- e. hydroxyalkyl,

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- f. substituted aryl,
  - g. heterocyclyl,
  - h. heterocyclalkyl,
  - i. heterocyclamino,
  - j. substituted heterocyclyl, and
  - k. substituted heterocyclalkyl,

or where  $\text{NR}_{10}\text{R}_{11}$  is heterocyclyl or substituted heterocyclyl, where substituents are independently selected from

- 1) alkyl,
- 2) alkoxy,
- 3) alkoxyalkyl,
- 4) cycloalkyl,
- 5) aryl,
- 6) heterocyclyl,
- 7) heterocyclcarbonyl,
- 8) heterocyclalkylaminocarbonyl,
- 9) hydroxy,
- 10) hydroxyalkyl,
- 11) hydroxyalkoxyalkyl,
- 12) carboxy,

- 13) carboxyalkyl,  
14) carboxycarbonyl,  
15) carboxaldehyde,  
16) alkoxycarbonyl,  
17) arylalkoxycarbonyl,  
18) aminoalkyl,  
19) aminoalkanoyl,  
20) carboxamido,  
21) alkoxycarbonylalkyl,  
22) carboxamidoalkyl,  
23) cyano,  
24) tetrazolyl,  
25) substituted tetrazolyl,  
26) alkanoyl,  
27) hydroxyalkanoyl,  
28) alkanoyloxy,  
29) alkanoylamino,  
30) alkanoyloxyalkyl,  
31) alkanoylaminoalkyl,  
32) sulfonate,  
33) alkylsulfonyl,  
34) alkylsulfonylaminocarbonyl,

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35) arylsulfonylaminocarbonyl, and

36) heterocyclysulfonylaminocarbonyl,

and wherein **Ar** is a substituted aryl or substituted heteroaryl group, where

5 substitutions are independently selected from

- a. hydrogen,
- b. halogen,
- c. alkyl,
- 10 d. aryl,
- e. haloalkyl,
- f. hydroxy,
- g. alkoxy,
- h. alkoxyalkyl,
- 15 i. alkoxycarbonyl,
- j. alkoxyalkoxy,
- k. hydroxyalkyl,
- l. aminoalkyl,
- m. aminocarbonyl,
- 20 n. alkyl(alkoxycarbonylalkyl)aminoalkyl,
- o. heterocyclyl,
- p. substituted heterocyclyl,

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- q. heterocyclalkyl,  
r. substituted heterocyclalkyl,  
s. carboxaldehyde,  
t. carboxaldehyde hydrazone,  
u. carboxamide,  
v. alkoxycarbonylalkyl,  
w. carboxy,  
x. carboxyalkyl,  
y. carboxy alkoxy,  
z. carboxythioalkoxy,  
aa. carboxycycloalkoxy,  
bb. thioalkyl,  
cc. hydroxycarbonylalkyl (carboxyalkyl),  
dd. hydroxyalkylaminocarbonyl,  
ee. cyano,  
ff. amino,  
gg. heterocyclalkylamino,  
hh. carboxyalkylamino,  
ii. heterocyclalkylaminocarbonyl, and  
jj. "trans-cinnamide".

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Additionally provided are methods of treatment or prophylaxis in which the inhibition of inflammation or suppression of immune response is desired, comprising administering an effective amount of a compound of formula I.

Still further provided are pharmaceutical compositions containing compounds  
5 of formula I.

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**Detailed Description**

The term "alkanoyl" as used herein refers to an alkyl group attached to the parent molecular group through a carbonyl group.

5 The term "alkanoylamino" as used herein refers to an alkanoyl group attached to the parent molecular group through an amino group.

The term "alkanoylaminoalkyl" as used herein refers to an alkanoylamino group attached to the parent molecular group through an alkyl group.

The term "alkanoyloxy" as used herein refers to an alkanoyl group attached to the parent molecular group through an oxygen radical.

10 The term "alkanoyloxyalkyl" as used herein refers to an alkanoyloxy group attached to the parent molecular group through an alkyl group.

The term "alkoxy" as used herein refers to an alkyl group attached to the parent molecular group through an oxygen atom.

15 The term "alkoxyalkoxy" as used herein refers to an alkoxy group attached to the parent molecular group through an alkoxy group.

The term "alkoxyalkyl" as used herein refers to an alkoxy group attached to the parent molecular group through an alkyl group.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group attached to the parent molecular group through a carbonyl group.

20 The term "alkoxycarbonylalkyl" as used herein refers to an alkoxycarbonyl group attached to the parent molecular group through an alkyl group.

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The term "alkyl" as used herein refers to a saturated straight or branched chain group of 1-10 carbon atoms derived from an alkane by the removal of one hydrogen atom.

The term "alkyl(alkoxycarbonylalkyl)amino" as used herein refers to an amino group substituted with one alkyl group and one alkoxycarbonylalkyl group.

The term "alkyl(alkoxycarbonylalkyl)aminoalkyl" as used herein refers to an alkyl(alkoxycarbonylalkyl)amino group attached to the parent molecular group through an alkyl group.

The term "alkylene" as used herein refers to a divalent group of 1-10 carbon atoms derived from a straight or branched chain alkane by the removal of two hydrogen atoms.

The term "alkylsulfonyl" as used herein refers to an alkyl radical attached to the parent molecular group through an  $-SO_2-$  group.

The term "alkylsulfonylaminocarbonyl" as used herein refers to an alkylsulfonyl group attached to the parent molecular group through an aminocarbonyl group.

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The term "amino" as used herein refers to a radical of the form  $-NR_{18}R_{19}$ , or to a radical of the form  $-NR_{18}-$ , where  $R_{18}$  and  $R_{19}$  are independently selected from hydrogen, alkyl or cycloalkyl.

The term "aminoalkanoyl" as used herein refers to an amino group attached to the parent molecular group through an alkanoyl group.

The term "aminoalkyl" as used herein refers to an amino group attached to the parent molecular group through an alkyl group.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group.

5      The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings. The aryl group can also be fused to a cyclohexane, cyclohexene, cyclopentane or cyclopentene ring. The aryl groups of this invention can be optionally substituted with alkyl, halogen, hydroxy, carboxy, or alkoxy substituents.

10      The term "arylalkoxy" as used herein refers to an aryl group attached to the parent molecular group through an alkoxy group.

The term "arylalkoxycarbonyl" as used herein refers to an arylalkoxy group attached to the parent molecular group through a carbonyl group.

15      The term "arylsulfonyl" as used herein refers to an aryl radical attached to the parent molecular group through an  $-SO_2-$  group.

The term "arylsulfonylaminocarbonyl" as used herein refers to an arylsulfonyl group attached to the parent molecular group through an aminocarbonyl group.

The term "carboxaldehyde" as used herein refers to the radical  $-CHO$ .

20      The term "carboxaldehyde hydrazone" as used herein refers to the radical  $-CH=N-NR_{20}R_{21}$ , where  $R_{20}$  and  $R_{21}$  are independently selected from hydrogen, alkyl or cycloalkyl.

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The terms "carboxamide" or "carboxamido" as used herein refer to an amino group attached to the parent molecular group through a carbonyl group.

The term "carboxamidoalkyl" as used herein refers to a carboxamido group attached to the parent molecular group through an alkyl group.

5 The term "carboxy" as used herein refers to the radical -COOH.

The term "carboxyalkyl" as used herein refers to a carboxy group attached to the parent molecular group through a alkyl group.

The term "carboxycarbonyl" as used herein refers to a carboxy group attached to the parent molecular group through a carbonyl group.

10 The term "cyano" as used herein refers to the radical -CN.

The term "cycloalkyl" as used herein refers to a monovalent saturated cyclic or bicyclic hydrocarbon group of 3-12 carbons derived from a cycloalkane by the removal of a single hydrogen atom. Cycloalkyl groups may be optionally substituted with alkyl, alkoxy, halo, or hydroxy substituents.

15 The terms "halo" or "halogen" as used herein refers to F, Cl, Br, or I.

The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms.

The terms "heterocycle" or "heterocyclyl" represent a 4-, 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The 4- and 5-membered rings have zero to two double bonds and the 6- and 7-membered rings have zero to three double bonds. The term "heterocycle" or "heterocyclic" as used herein additionally refers to bicyclic,

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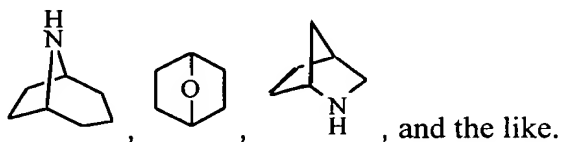
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tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring or another monocyclic heterocyclic ring. Heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, triazolyl, and the like.

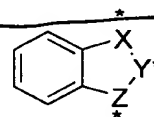
Heterocyclics also include bridged bicyclic groups where a monocyclic

15 heterocyclic group is bridged by an alkylene group such as



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Heterocyclics also include compounds of the formula



where X\*

and Z\* are independently selected from -CH<sub>2</sub>-, -CH<sub>2</sub>NH-, -CH<sub>2</sub>O-, -NH- and -O-,

20 with the proviso that at least one of X\* and Z\* is not -CH<sub>2</sub>-, and Y\* is selected from

5 ~~-C(O)- and -(C(R''))<sub>v</sub> -, where R'' is hydrogen or alkyl of one to four carbons, and v is 1-3. These heterocycles include 1,3-benzodioxolyl, 1,4-benzodioxanyl, 1,3-benzimidazol-2-one and the like. The heterocycle groups of this invention can be optionally substituted with alkoxy, alkyl, halogen, hydroxy, carboxy, carboxyalkyl, or alkoxycarbonyl substituents.~~

The term "heterocyclylalkyl" as used herein refers to an heterocyclic group attached to the parent molecular group through an alkyl group.

10 The term "heterocyclylalkylamino" as used herein refers to an heterocyclylalkyl group attached to the parent molecular group through an amino group.

The term "heterocyclylalkylaminocarbonyl" as used herein refers to a heterocyclylalkylamino group attached to the parent molecular group through a carbonyl group.

15 The term "heterocyclylamino" as used herein refers to a heterocyclyl group attached to the parent molecular group through a amino group.

The term "heterocyclylcarbonyl" as used herein refers to a heterocyclyl group attached to the parent molecular group through a carbonyl group.

The term "heterocyclylsulfonyl" as used herein refers to a heterocyclyl radical attached to the parent molecular group through an -SO<sub>2</sub>- group.

20 The term "heterocyclylsulfonylaminocarbonyl" as used herein refers to a heterocyclylsulfonyl group attached to the parent molecular group through an aminocarbonyl group.

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The term "hydroxyalkanoyl" as used herein refers to an hydroxy radical attached to the parent molecular group through an alkanoyl group.

The term "hydroxyalkoxy" as used herein refers to an hydroxy radical attached to the parent molecular group through an alkoxy group.

5 The term "hydroxyalkoxyalkyl" as used herein refers to an hydroxyalkoxy group attached to the parent molecular group through an alkyl group.

The term "hydroxyalkyl" as used herein refers to an hydroxy radical attached to the parent molecular group through an alkyl group.

10 The term "hydroxyalkylaminocarbonyl" as used herein refers to an hydroxyalkyl group attached to the parent molecular group through an aminocarbonyl group.

The term "perfluoroalkyl" as used herein refers to an alkyl group in which all of the hydrogen atoms have been replaced by fluoride atoms.

15 The term "phenyl" as used herein refers to a monocyclic carbocyclic ring system having one aromatic ring. The phenyl group can also be fused to a cyclohexane or cyclopentane ring. The phenyl groups of this invention can be optionally substituted with alkyl, halogen, hydroxy or alkoxy substituents.

20 The term "pharmaceutically-acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like,

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commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

The term "prodrug," as used herein, represents compounds which are rapidly transformed *in vivo* to the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

10 Sub A9 The term "sulfonate" as used herein refers to the radical  $-\text{SO}_3\text{H}$

The term "tetrazole" or "tetrazolyl" as used herein refers to the heterocyclic radical  $-\text{CN}_4\text{H}$ .

The term "thioalkoxy" as used herein refers to an alkyl group attached to the parent molecular group through a sulfur atom.

15 Compounds of the present invention can exist as stereoisomers wherein asymmetric or chiral centers are present. These compounds are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. The present invention contemplates various stereoisomers and mixtures thereof. Stereoisomers include enantiomers and diastereomers, and mixtures of  
20 enantiomers or diastereomers are designated ( $\pm$ ). Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by

5 liberation of the optically pure product from the auxiliary, (2) salt formation  
employing an optically active resolving agent, or (3) direct separation of the mixture  
of optical enantiomers on chiral chromatographic columns.

Geometric isomers can also exist in the compounds of the present invention.

thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the Z or E configuration wherein the term "Z" represents substituents on the same side of the carbon-carbon double bond and the term "E" represents substituents on opposite sides of the carbon-carbon double bond. The arrangement of substituents around a carbocyclic ring are designated as cis or trans wherein the term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated cis/trans.

As is apparent from the foregoing descriptions, the compounds of Formula 1 are useful in a variety of forms, i.e., with various substitutions as identified.

10           Compounds of the present invention include:

(2,4-Dichlorophenyl)[2-(*E*-((3-(1-imidazolyl)propylamino)carbonyl)ethenyl)phenyl].

(2,4-Dichlorophenyl)[2-chloro-4-( *E*-((2-

sulfide;

sulfide;

20 phenyl] sulfide;

ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl)ethenyl)phenyl]  
sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-( *E*-((4-methylpiperazin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;

5 (2,4-Dichlorophenyl)[2-chloro-4-( *E*-((4-acetyl) piperazin-1-  
yl)carbonyl)ethenyl)phenyl]  
sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-( *E*-((4-(2-pyridyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide;

10 (2-(Hydroxymethyl)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl)  
ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-chloro-4-( *E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide;

15 (2,4-Dichlorophenyl)[2-chloro-4-( *E*-((4-(2-hydroxyethoxyethyl)piperazin-1-  
yl)carbonyl) ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-( *E*-((3-(hydroxymethyl)piperidin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-( *E*-((2-(hydroxymethyl)piperidin-1-yl)carbonyl)

20 ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-( *E*-((3-acetamidopyrrolidin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;

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- 5 (2-Bromophenyl)[2-chloro-4-( *E*-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl]  
sulfide;
- (2-Bromophenyl)[2-chloro-4-( *E*-((piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;
- (2,4-Dichlorophenyl)[2-chloro-4-( *E*-((3-carboxypiperidin-1-  
5 yl)carbonyl)ethenyl)phenyl] sulfide;
- (2,4-Dichlorophenyl)[2-chloro-4-( *E*-((4-carboxypiperidin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;
- (2-Bromophenyl)[2-chloro-4-( *E*-((4-acetylhomopiperazin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;
- 10 (2-Bromophenyl)[2-chloro-4-( *E*-((thiomorpholin-1-yl)carbonyl)ethenyl)phenyl]  
sulfide;
- (2-Bromophenyl)[2-chloro-4-( *E*-((4-(1-benzimidazol-2-onyl)piperidin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide;
- (2-Bromophenyl)[2-chloro-4-( *E*-((2-  
15 tetrahydroisoquinoliny)carbonyl)ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-( *E*-((4-acetyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-( *E*-((1-morpholiny)carbonyl)ethenyl)phenyl]  
sulfide;
- 20 (2-Methylphenyl)[2-trifluoromethyl-4-( *E*-((2-(1-morpholiny)ethylamino)carbonyl)  
ethenyl)phenyl] sulfide;
- (2-Methylphenyl)[2-trifluoromethyl-4-( *E*-((4-phenylpiperazin-1-yl)carbonyl)

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(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(diethylaminocarbonyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide;

5 yl)carbonyl) ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxymethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Chlorophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]  
sulfide;

15 sulfide;

(2-Ethylphenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]  
sulfide;

(2-*tert*-Butylphenyl)[2-nitro-4-( *E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl]

sulfide;

(2-Chlorophenyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl))2-propenyl]phenyl] sulfide;

(2-(1-Morpholinylmethyl)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-(4-(1,3-Benzodioxolyl-5-methyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-(4-(*iso*-Propylaminocarbonylmethyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-((*N*-Ethoxycarbonylmethyl-*N*-methyl)aminomethyl)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-Formylphenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

(2-(4-Formylpiperazin-1-ylmethyl)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

(2-( *E*-((1-Morpholinyl)carbonyl)ethenyl)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

(2-Formylphenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Formylphenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide,

*N,N*-dimethyl hydrazone;

(2-((3-(1-Morpholinyl)propyl)-1-amino)phenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl) ethenyl)phenyl] sulfide;

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(2,4-Dichlorophenyl)[2-bromo-4-( *E*-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)ethenyl)phenyl] sulfide;

(2,4-Dichlorophenyl)[2-formyl-4-( *E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;

5 (2-Chloro-6-formylphenyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Cyanophenyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (2-Isopropylphenyl)[2-cyano-4-( *E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Bromophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-(Pyrrolidin-1-yl)phenyl)[2-chloro-4-( *E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (2-Methoxyphenyl)-[2-chloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carbomethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Methylphenyl)[2-nitro-4-( *E*-((3-carboxamido-4-carbobenzoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2-nitro-4-( *E*-((2-carbomethoxy-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(2-Isopropylphenyl)[2-nitro-4-( *E*-((2-carboxy-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-((morpholin -1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-((cyclobutylamino)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-((cyclopentylamino)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-((5-hydroxypent-1-ylamino)carbonyl)ethenyl) phenyl] sulfide;

15 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carbomethoxy-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Biphenyl)[2-chloro-4-( *E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3,4-Dimethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-trifluoromethyl-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(5-Indolyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(5-Benzodioxolyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-nitro-4-( *E*-((2-carbomethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2,3-Dimethoxyphenyl)-[2-chloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Fluorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-trifluoromethyl-4-( *E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-(Pyrrolidin-1-yl)phenyl)[2-trifluoromethyl-4-( *E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (3-Carboxamidophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3-(Hydroxymethyl)phenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

Phenyl[2-trifluoromethyl-4-( *E*-((4-(*tert*-butoxycarbonyl)piperazin-1-

20 yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-((2-carbomethoxy-4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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- (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(pyridine-4-methylaminocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- (2-Ethoxyphenyl)-[2-chloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide;
- (2-Methoxyphenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;
- 5 (2-(Azetidin-1-yl)phenyl)[2-trifluoromethyl-4-( *E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- (2-(Piperidin-1-yl)phenyl)[2-trifluoromethyl-4-( *E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- 10 (3-Chloro-2-formylphenyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- (2-Trifluoromethylphenyl)[2-trifluoromethyl-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- (3-Bromophenyl)[2-trifluoromethyl-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- 15 (3,5-Dimethylphenyl)[2-trifluoromethyl-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-dimethylaminocarbonyl-4-(pyridine-4-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;
- 20 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-dimethylaminocarbonyl-4-carbomethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(1-morpholinocarbonyl)-4-*tert*-  
butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-dimethylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(dimethylaminocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (2-Bromophenyl)[2-chloro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)  
ethenyl)phenyl]sulfide;

(2-[2-Methoxy]ethoxyphenyl)-[2-chloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(morpholinocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-nitro-4-( *E*-(4-(pyridine-4-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(pyridine-3-methylaminocarbonyl)-4-*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(pyridine-2-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(pyridine-3-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(4-Hydroxyphenyl)[2-nitro-4-( *E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

15 (3,5-Dichlorophenyl)[2-nitro-4-( *E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(5*S*-acetoxymethyl-pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

20 (2-Bromophenyl)[2-chloro-4-(*E*-((3-(5*S*-methoxymethyl-pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(4*R*-hydroxymethyl-pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

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- Phenyl[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;  
(2-Dimethylaminophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide;  
(3-((2-Hydroxyethyl)aminocarbonyl)phenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-  
5 yl)carbonyl)ethenyl) phenyl] sulfide;  
(3-((3-(1-Imidazolyl)propyl)aminocarbonyl)phenyl)[2-nitro-4-( *E*-((4-  
acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;  
(3-((2-(1-Morpholinyl)ethyl)aminocarbonyl)phenyl)[2-nitro-4-( *E*-((4-  
acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;  
10 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-hydroxymethyl-4-*tert*-  
butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;  
(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-formylpiperazin-1-yl)carbonyl)ethenyl) phenyl]  
sulfide;  
(2-Isopropylphenyl)[2-nitro-4-( *E*-((2-hydroxymethyl-4-*tert*-  
15 butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;  
(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(3-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl)  
phenyl]sulfide;  
(3- Aminophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-  
yl)carbonyl)ethenyl)phenyl]sulfide;  
20 (4-Aminophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-  
yl)carbonyl)ethenyl)phenyl]sulfide;

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(2,4-Dimethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2,5-Dimethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

5 (4-Methoxyphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(3-Chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

10 (2-Chloro, 4,5-diaminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3,4-Diaminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl]

(6-Chlorobenzimidazol-2-on-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (1-Methylindol-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Hydroxy, 4-aminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyridine-2-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-(pyridine-3-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((2-carbomethoxy-4-methoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-nitro-4-( *E*-((2-carboxy-4-methoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carbomethoxy-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (2-Ethoxyphenyl)-[2-chloro-4(*E*-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(2-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide;

15 (2-Ethoxyphenyl)[2-trifluoromethyl-4-( *E*-((1-(*tert*-butoxycarbonyl)-4-hydroxypyrrolidin-3-ylamino)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(2-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

20 (2-Ethoxyphenyl)[2-trifluoromethyl-4-( *E*-(((pyrrol-3-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl] sulfide;

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(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-(ethoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

5 (2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-(2-furylcarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(3-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl)phenyl]sulfide;

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-ethoxycarbonylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

15 (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-isopropoxycarbonylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-isobutoxycarbonylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-((1-propen-2-oxy)carbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-propionylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

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(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-carboxamidopiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-methylaminocarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-nitro-4-( *E*-((4-(pyrimidin-2-yl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-hydroxyacetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((4-(pyrazine-2-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-(((2-carboxypyrrol-3-in-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-hydroxymethyl-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-(((2-carboxypyrrol-3-in-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-trifluoromethyl-4-( *E*-(((2-hydroxymethylpyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2-nitro-4-( *E*-(((3-cyclopropylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carboxamidopiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carbomethoxy-4-oxopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3,5-dimethylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Ethylindol-7-yl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(3-[2-Methoxy]ethoxyphenyl)-[2-chloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

10 (2-Bromophenyl)[2-chloro-4-(*E*-((4,4'-*S*-dioxythiomorpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Bromophenyl)[2-chloro-4-(*E*-(*N*-carbomethoxymethyl-*N*-(3-(pyrrolidin-2-on-1-yl)prop-1-yl)amino)carbonyl) ethenyl)phenyl] sulfide;

15 (2-Bromophenyl)[2-chloro-4-(*E*-((4-*S*-oxythiomorpholin-1-yl)-2-pyrrolidinone)carbonyl) ethenyl)phenyl] sulfide;

(2-Methoxy-5-chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-acetoxymethyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3,5-dimethyl-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(1-Methylindol-5-yl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (Benzodioxan-6-yl)[2-nitro-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide;

(Benzodioxan-6-yl)[2-nitro-4-( *E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-( *E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*Z*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((6-methylpyrid-2-ylamino)carbonyl)ethenyl) phenyl] sulfide;

15 (2-Methyl-3-chlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-( *E*-((3-carboxamidopiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-( *E*-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-( *E*-((4-carboxamidopiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

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~~(Benzodioxan-6-yl)[2-nitro-4-( *E*-((4-*tert*-butoxycarbonyl)piperazin-1-yl)  
 carbonyl)ethenyl) phenyl] sulfide;  
 (2-Isopropylphenyl)[2-nitro-4-( *E*-((*syn*-3,5-dimethylmorpholin-1-  
 yl)carbonyl)ethenyl) phenyl] sulfide;  
 5 (2-Isopropylphenyl)[2-nitro-4-( *E*-((*anti*-3,5-dimethylmorpholin-1-  
 yl)carbonyl)ethenyl) phenyl] sulfide;  
 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carboethoxypiperazin-1-yl)carbonyl)ethenyl)  
 phenyl] sulfide;  
 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-isopropoxycarbonyl)piperazin-1-  
 10 yl)carbonyl)ethenyl) phenyl] sulfide;  
 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(dimethylaminocarbonyl)-4-methylpiperazin-1-  
 yl)carbonyl)ethenyl) phenyl] sulfide;  
 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carbomethoxy-4-hydroxypiperidin-1-  
 yl)carbonyl)ethenyl) phenyl] sulfide;  
 15 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-hydroxymethyl-4-hydroxypiperidin-1-  
 yl)carbonyl)ethenyl) phenyl] sulfide;  
 (2-Ethoxyphenyl)[2-trifluoromethyl-4-( *E*-((2-carbomethoxy-4-  
 (methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;  
 (2-Ethoxyphenyl)[2-trifluoromethyl-4-( *E*-((2-carbomethoxy-4-methyl piperazin-1-  
 20 yl)carbonyl)ethenyl) phenyl] sulfide;  
 (2-Ethoxyphenyl)[2-trifluoromethyl-4-( *E*-((2-carboxy-4-(methoxycarbonyl)piperazin-  
 1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

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~~(Indol-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(1-Ethyl,3-(dimethylaminomethyl)indol-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(5-Ethoxybenzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-~~

5 ~~yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(2-Ethyl-4-bromophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(Benzodioxan-6-yl)[2-nitro-4-(*E*-((2-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;~~

10 ~~(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-carboxymethylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;~~

~~(3-Morpholinophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(5-Ethoxybenzodioxan-8-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-~~

15 ~~yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(5-Chloro-8-ethoxyquinolin-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

20 ~~(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

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(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-ethanesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-(4-methylpiperazine)sulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-*p*-toluenesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-methyl-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Hydroxyphenyl)-[2-chloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

10 (1-(Carboxymethyl)indol-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(1-pyrrolidin-2-onyl)prop-1-ylamino)carbonyl)ethenyl) phenyl] sulfide;

(3-(2-Morpholinoethylamino)phenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Pyrrolidin-1-ylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (3-Bromophenyl)[2-nitro-4-(*E*-((3-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(3-Bromophenyl)[2-nitro-4-(*E*-((4-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-(Hydroxymethyl)-benzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

(3-(Dimethylaminomethyl)indol-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

15 (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((4-*p*-toluenesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxy-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-nitro-4-( *E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

5 (Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((2-carbomethoxy-4-*tert*-butoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((2-carbomethoxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((2-carbomethoxypiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

15 (2-Methyl-3-(carboethoxymethyl)indol-5-yl)[2-trifluoromethyl-4-( *E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-(2-Methoxyethyl)indol-5-yl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-acetoxymethyl-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(dimethylaminocarbonyl)-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-cyanomorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carboethoxymorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((2-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((4-carbomethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (Benzodioxan-6-yl)[2-trifluoro-4-(*E*-((4-(benzimidazol-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-(methylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((3-carbomethoxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carboxymorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carboxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

5 (Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (2-Isopropylphenyl)[2-nitro-4-(*E*-((2-(dimethylaminomethyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((piperidin-1-ylamino)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

15 (2-(Dimethylaminocarbonyl)-benzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide;;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(2-(methoxymethyl)tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20 (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(1-(methoxymethyl)tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-(1-pyrrolidin-2-onyl)propylamino) carbonyl)ethenyl) phenyl] sulfide;

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(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

5 (1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

10 (1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((2-(1-methylpyrrolidin-2-yl)ethylamino)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-sulfopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-

20 ((ethanesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-(*p*-toluenesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

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(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((4-  
((ethanesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;  
(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2(tetrazol-5-yl)morpholin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide;  
5 (2-Isopropylphenyl)[2-nitro-4-( *E*-((2-butyl, 5-(tetrazol-5-yl)morpholin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide;  
(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide;  
(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(*E*-((3-(pyrrolidin-2-on-1-  
10 yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;  
(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-  
(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;  
(3-Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-  
ylamino)carbonyl) ethenyl)phenyl]sulfide;  
15 (Benzodioxan-6-yl)[2-chloro-4-( *E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)  
phenyl]  
(2-(and 3-)(Aminomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-(pyrrolidin-  
2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;  
(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(methylaminocarbonyl)morpholin-1-  
20 yl)carbonyl)ethenyl) phenyl] sulfide;  
(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(hydroxymethyl)morpholin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide;

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~~(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(acetoxymethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(aminomethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

5 ~~(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-(acetamidomethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide;~~

~~(Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;~~

10 ~~(Benzodioxan-6-yl)[2-chloro-4-( *E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;~~

~~(Benzodioxan-6-yl)[2-chloro-4-( *E*-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide~~

~~(2-Methoxyphenyl)-[2,3-dichloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;~~

15 ~~(2-Methoxyphenyl)-[2,3-dimethyl-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;~~

~~(2-Isopropylphenyl)[2-nitro-4-(*E*-((indol-5-ylamino)carbonyl)ethenyl) phenyl] sulfide;~~

20 ~~(Benzodioxan-6-yl)[2-chloro-4-( *E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;~~

~~(Benzodioxan-6-yl)[2-chloro-4-( *E*-((3-(tetrazol-5-yl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;~~

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 (Benzodioxan-6-yl)[2-chloro-4-( *E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-( *E*-((2-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

5 (Benzodioxan-6-yl)[2-chloro-4-( *E*-((3-(tetrazol-5-yl)morpholin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-( *E*-((4-(methylaminocarbonyl)piperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

10 (2-Methoxyphenyl)-[2,3-dichloro-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-chloro-4-( *E*-((4-(tetrazol-5-yl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(2-Methoxyphenyl)-[3-chloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide;

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-oxopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

15 (Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((3-*R*-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( *E*-((3-*R*-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide;

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~~(Benzodioxan-6-yl)[2,3-dichloro-4-( *E*-((4-acetylpiperazin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide;~~

~~(Benzodioxan-6-yl)[2,3-dichloro-4-( *E*-((3-carboethoxypiperidin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide;~~

5 ~~(Benzodioxan-6-yl)[2,3-dichloro-4-( *E*-((4-carboethoxypiperidin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide;~~

~~(Benzodioxan-6-yl)[2,3-dichloro-4-( *E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide;~~

10 ~~(Benzodioxan-6-yl)[2,3-dichloro-4-( *E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide;~~

~~(2-Isopropylphenyl)[2,3-dichloro-4-( *E*-((3-(1-pyrrolidin-2-onyl)propylamino)  
carbonyl)ethenyl) phenyl] sulfide;~~

~~(2-Isopropylphenyl)[2,3-dichloro-4-( *E*-((4-acetylpiperazin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide;~~

15 ~~(2-Isopropylphenyl)[2,3-dichloro-4-( *E*-((3-carboethoxypiperidin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide;~~

~~(2-Isopropylphenyl)[2,3-dichloro-4-( *E*-((4-carboethoxypiperidin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide;~~

20 ~~(2-Isopropylphenyl)[2,3-dichloro-4-( *E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide;~~

~~(2-Isopropylphenyl)[2,3-dichloro-4-( *E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide;~~

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(1-Methylindol-5-yl)[2,3-dichloro-4-( *E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2,3-dichloro-4-( *E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

5 (1-Methylindol-5-yl)[2,3-dichloro-4-( *E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

(1-Methylindol-5-yl)[2,3-dichloro-4-( *E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide;

10 (2-Ethoxyphenyl)-[2,3-dichloro-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide;

(2-Ethoxyphenyl)-[2,3-dichloro-4(*E*-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

(2-Ethoxyphenyl)-[2,3-dichloro-4(*E*-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide;

15 (2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2-nitro-4-( *E*-((3-carboxypyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

20 (2-Isopropylphenyl)[2,3-difluoro-4-( *E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

(2-Isopropylphenyl)[2,3-difluoro-4-( *E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide;

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(2-Isopropylphenyl)[2,3-difluoro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-ethoxycarbonylpyrrolidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

5 (Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboxypyrrolidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

10 (2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(Benzodioxan-6-yl) [4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)naphthyl] sulfide;

15 (2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-(spiro-hydantoin-5-yl)-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

20 (2-Methoxyphenyl)[2,3-dichloro-4-(*E*-((4-ethylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

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(Benzodioxan-6-yl)[2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(E-((4-(carboxymethylamino)carbonyl-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

5 (2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-carboxymethylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-N-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-( E-((4-(carbo-2,3-  
10 dihydroxypropylamino)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(E-(4-(2,3-dihydroxypropionyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-( E-(4-(2,3-dihydroxy-3-carboxypropionyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

15 (1-Methylindol-5-yl) [2,3-dichloro-4-(E-((4-(carboxymethylamino)carbonyl-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(E-((4-sulfopiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(E-(4-methylhomopiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

20 (1-Methylindol-5-yl) [2,3-dichloro-4-(E-(4-tetrahydrofuroyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

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(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-amino-4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-dichloro-4-((4-furoylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

5 (1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-(carbo-3-sulfopropylamino)piperadin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[ 2,3-dichloro-4-(*E*-(4-acetylamino-4-carboxypiperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

10 (2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) 5-[8-(*E*-((4-(aminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)quinoliny] sulfide;

(2-Methoxyphenyl) [2-trifluoromethyl-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

15 (1-Methylindol-5-yl) [ 2,3-dichloro-4-(*E/Z*-((1*S*,4*S*)-2,5-diazabicyclo(2,2,1)heptan-2-ylcarbonyl)ethenyl)-2,3-dichlorophenyl] sulfide;

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-hydroxy-3-carboxypiperadin-1-ylcarbonyl)ethenyl)phenyl] sulfide;;

20 (1-Methylindol-5-yl) [ 2,3-dichloro-4-(*E*-(*S*-oxothiomorpholin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-sulfophenylamino)carbonyl)ethenyl)phenyl] sulfide;

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~~(2-Methoxyphenyl) [2,3-dichloro-4-(E-((4-~~

~~carboxyphenylamino)carbonyl)ethenyl)phenyl] sulfide;~~

~~[3-(4-Morpholino)phenyl] [2,3-dichloro-4-(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;~~

5 ~~[3-(4-Morpholino)phenyl] [2,3-dichloro-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;~~

~~(2-Methoxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-phenylcarboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;~~

10 ~~(2-Methoxyphenyl) [2,3-dichloro-4-(E-(((4-hydroxylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;~~

~~(2-Methoxyphenyl) [2,3-dichloro-4-(E-((N-carboxymethyl-N-phenylamino)carbonyl)ethenyl)phenyl] sulfide;~~

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(2-Methoxyphenyl) [3-chloro-6-hydroxy-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(E-(4-((1-(2-phenyl-1-carboxyethyl)amino)carbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

5 (2-Methoxyphenyl) [2,3-dichloro-4-(E-(4-((1-(2-hydroxy-1-carboxyethyl)amino)carbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(3-(1-(3-Carboxypiperidinyl)phenyl)[2,3-dichloro-4-(E-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

10 (3-(4-Pyrrolidin-1-yl)piperidin-1-yl)phenyl) [2,3-dichloro-4-(E-(((3-(2-pyrrolidinon-1-yl)propylamino)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-(Spiro-2,2-dioxolanyl)piperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl]sulfide;

[3-(3-Carboxylpiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

15 (2-(2-Carboxy)ethenyl)phenyl) [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxylpiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(1,2,3,6-tetrahydropyridine)-1-yl)carbonyl]ethenyl)phenyl] sulfide;

20 [3-(4-Carboxylpiperidinyl)phenyl] [2,3-dichloro-4-(E-[(4-morpholinyl)carbonyl]ethenyl)phenyl] sulfide;

[2-(4-Acetylpiperazin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

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3-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-morpholinyl)carbonyl]ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-(dimethylaminosulfamoyl)piperazin-1-yl)carbonyl]ethenyl)phenyl] sulfide;

5 (2-Methoxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((2-carboxypyrrolidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

10 [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-((trifluoromethylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Methoxyphenyl)[2,3-dichloro-4-(E-(piperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide;

(2-Hydroxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

15 (2-Methoxyphenyl) [2,3-dichloro-4-(E-(((4-carboxyphenyl)methyl)amino)carbonyl)ethenyl)phenyl]sulfide;

(2-Methoxyphenyl) [2,3-dichloro-4-(E-(((4-pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

(2-Hydroxyphenyl)[2,3-dichloro-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide;

20

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-((methylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

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(2-Aminophenyl) [2,3-dichloro-4-(*E*-((4-morpholinyl)carbonyl)ethenyl)phenyl]  
sulfide;

(3-(4-carboxypiperidin-1-yl)phenyl)[2,3-dichloro-4-(*E*-((S-oxothiomorpholin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;

5 [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-hydroxypiperidin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;

(2-Glycoxyphenyl) [2,3-dichloro-4-(*E*-((4-  
morpholino)carbonyl)ethenyl)phenyl]sulfide;

10 (2-(4-Butyroxyl)phenyl)[2,3-dichloro-4-(*E*-((4-  
morpholino)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-hydroxyethylpiperazin-  
1-yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-furoylpiperazin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;

15 [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((pyrrolidin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-  
((diethylaminocarbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-ethylpiperazin-  
20 yl)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-  
(aminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

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~~[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-(2-ethoxyethyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;~~

~~[3-((4-Carboxymethyl)piperazin-1-yl)phenyl] [(2,3-dichloro-4-(E-(4-morpholinyl)carbonyl)ethenyl)phenyl] sulfide;~~

5 ~~[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;~~

~~(3-Hydroxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;~~

~~[3-(4-Butyroxyl)phenyl] [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;~~

~~(2-Hydroxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;~~

~~(3-Hydroxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;~~

15 ~~[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide;~~

~~[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl] sulfide;~~

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[2-((4-Carboxy)butyloxy)phenyl] [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

(2-Glycoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

5 (2-(4-Butyroxyl)phenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-ditrifluoromethyl-4-(E-((bis-(2-ethoxyethyl)amino)carbonyl)ethenyl)phenyl] sulfide;

10 [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis-(trifluoromethyl)-4-(E-((bis-(2-hydroxypropyl)amino)carbonyl)ethenyl)phenyl] sulfide;

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis-(trifluoromethyl)-4-(E-((piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

(3-(4-Butyroxyl)phenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide;

15 [2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(3-(2-pyrrolidinon-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide;

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-[(3-(2-pyrrolidinon-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide;

20 [2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

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[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide;

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(*E*-((4-(2-(hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide; and

5 (3-(3-Propoxy)phenyl) [2,3-dichloro-4-(*E*-((4-morpholino)carbonyl)ethenyl)phenyl] sulfide.

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Pharmaceutical Compositions and Methods of Treatment

The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more pharmaceutically-acceptable carriers. The pharmaceutical compositions may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal administration.

The pharmaceutical compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray. The term "parenteral" administration as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically-acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

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These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like, Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

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In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

5 Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically-acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders such as, for example, 10 carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants such as glycerol, (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, (e) solution retarding agents such as paraffin, (f) absorption accelerators such as quaternary ammonium compounds, (g) wetting agents such as, for example, 15 cetyl alcohol and glycerol monostearate, (h) absorbents such as kaolin and bentonite clay, and (I) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

20 Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

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The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically-acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

5 Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically-acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott,  
20 Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y.  
(1976), p. 33 et seq.

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5 The compounds of the present invention may be used in the form of pharmaceutically-acceptable salts derived from inorganic or organic acids. By "pharmaceutically-acceptable salt" is meant those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically-acceptable salts are well-known in the art. For example, S. M. Berge, *et al.* Describe pharmaceutically-acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 et seq. The salts may be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate (isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides

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and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically-acceptable basic addition salts include cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

Dosage forms for topical administration of a compound of this invention include powders, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically-acceptable carrier and any needed preservatives, buffers, or propellants which may be required. Ophthalmic

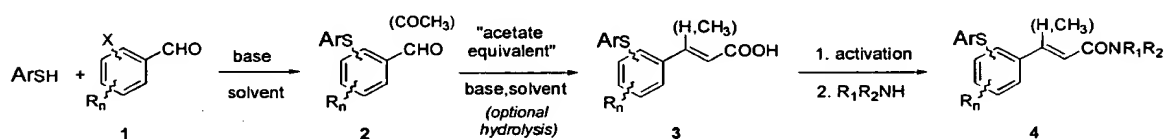
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Preparation of Compounds of the Invention

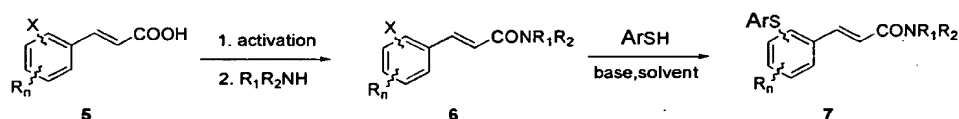
The compounds and processes of the present invention may be better understood in connection with the following synthetic Schemes which illustrate the methods by which the compounds of the invention can be prepared.

Scheme 1

Scheme 1 describes the synthesis of a typical cinnamide-substituted diaryl sulfide **4** through an aldehyde intermediate **2**. Aldehyde **2** is prepared by reaction of a thiophenol (for example 2,4-dichlorothiophenol, 2-bromothiophenol, or the like) with halo-substituted benzaldehyde derivative **1** (e.g. 2-chlorobenzaldehyde, 3-chloro,4-fluorobenzaldehyde, or the like) in the presence of base (e.g. sodium carbonate, triethylamine, or the like) and a polar solvent (e.g. dimethylformamide, dimethylsulfoxide, or the like). The aldehyde group is homologated to the corresponding cinnamic acid **3**, using an acetate equivalent (for example, malonic acid, triethoxyphosphonoacetate, or the like) in the presence of an appropriate base and solvent. In some cases, it may be necessary to hydrolyze an intermediate ester (for example using sodium hydroxide in alcohol). The acid group is activated (for

example using thionyl chloride, or dicyclohexylcarbodiimide and N-hydroxysuccinimide, or the like) and reacted with a primary or secondary amine (for example, 6-aminohexanol, pyrrolidone-3-propylamine, or the like) to provide the desired analog 4. In one variant, a halo-acetophenone can replace benzaldehyde 2; the resultant cinnamides 4 are substituted with a methyl group at the 3-position.

Scheme 2

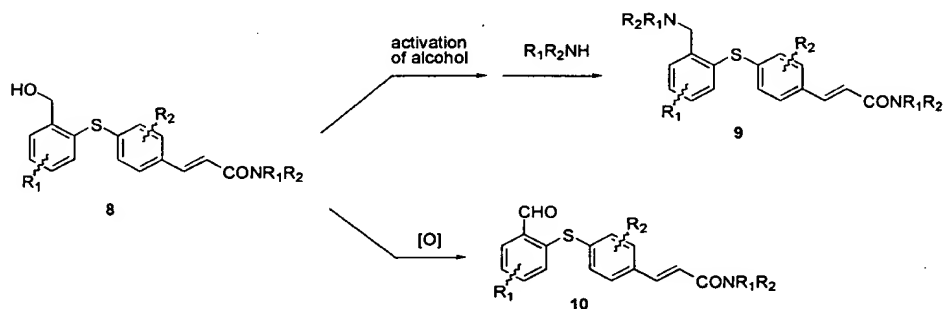


Alternatively, the order of these coupling steps may be reversed (Scheme 2).

A substituted halocinnamic acid 5 (e.g. 3-chloro-2-nitrocinnamic acid or the like) may be coupled with a primary or secondary amine (e.g. N-acetylpiperazine or the like) as described above to give the corresponding amide 6. The halo-group can then be displaced with a substituted thiophenol in the presence of base to provide the product

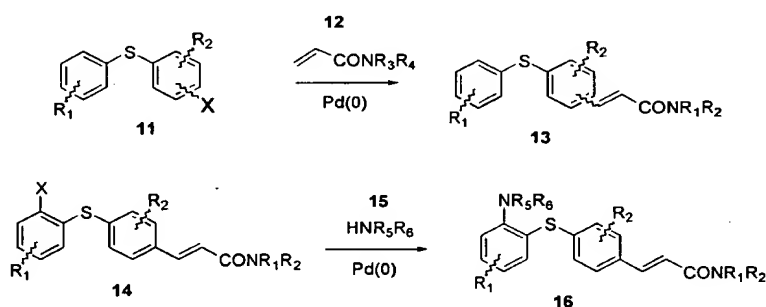
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Scheme 3



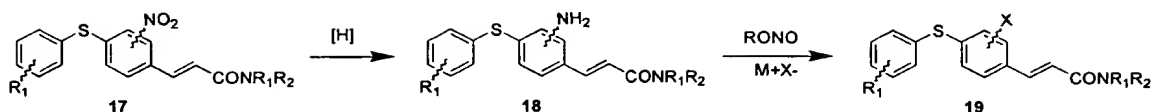
A number of the compounds described herein may be prepared from intermediate benzylic alcohols like **8** (Scheme 3). Activation of the alcohol moiety (for example, using phosphorus tribromide or methanesulfonyl chloride and lithium halide in dimethylformamide) and displacement with a primary or secondary amine (e.g. morpholine, N-formylpiperazine or the like) provides analogs with structures related to **9**. Alternatively the alcohol may be oxidized (for example using TPAP or PCC or the like) to give aldehyde **10**.

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Scheme 4

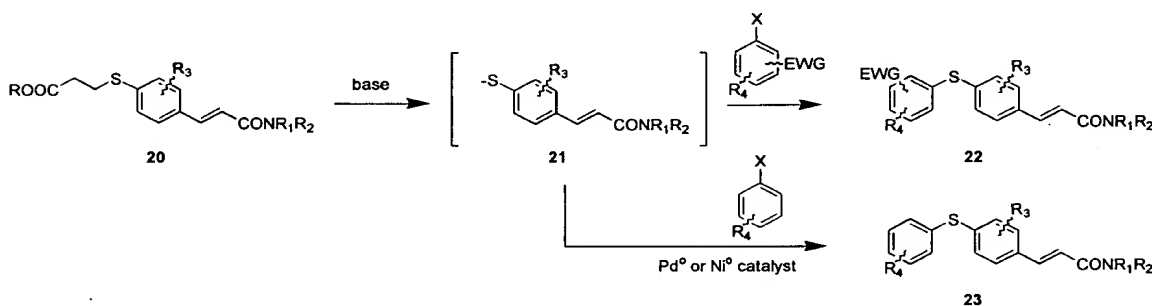
Cinnamides like **13** may be prepared from halo-substituted derivatives **11** by palladium-mediated coupling [e.g. using tetrakis (o-tolyl phosphine) palladium (0),  $Pd_2(dba)_3$ , or the like] with acrylamide derivatives **12** (Scheme 4). In similar manner, anilino-cinnamides like **16** can be prepared by palladium-mediated coupling of amines **15** with halo-cinnamides **14**.

## Scheme 5



- 5 In some cases, functional groups on the aromatic rings can be modified to produce new analogs (Scheme 5). For example, a nitro group in compounds like **17** may be reduced (for example, with tin(II) chloride, or by catalytic hydrogenation, or the like) to the corresponding amine **18**. This amine may then itself be converted to a halogen, for example by diazotization using nitrous acid or t-butyl nitrite in the
- 10 presence of a metal halide salt like cupric bromide, providing analog **19**.

## Scheme 6



- 15 It is also possible to assemble cinnamide-substituted diaryl sulfides in a “reverse” sense (Scheme 6). Thus, for example, compound **20**, prepared as described in Scheme 1, may be deprotected by treatment with base (e.g. potassium t-butoxide or the like) to provide thiolate anion **21**, which may be reacted with an activated

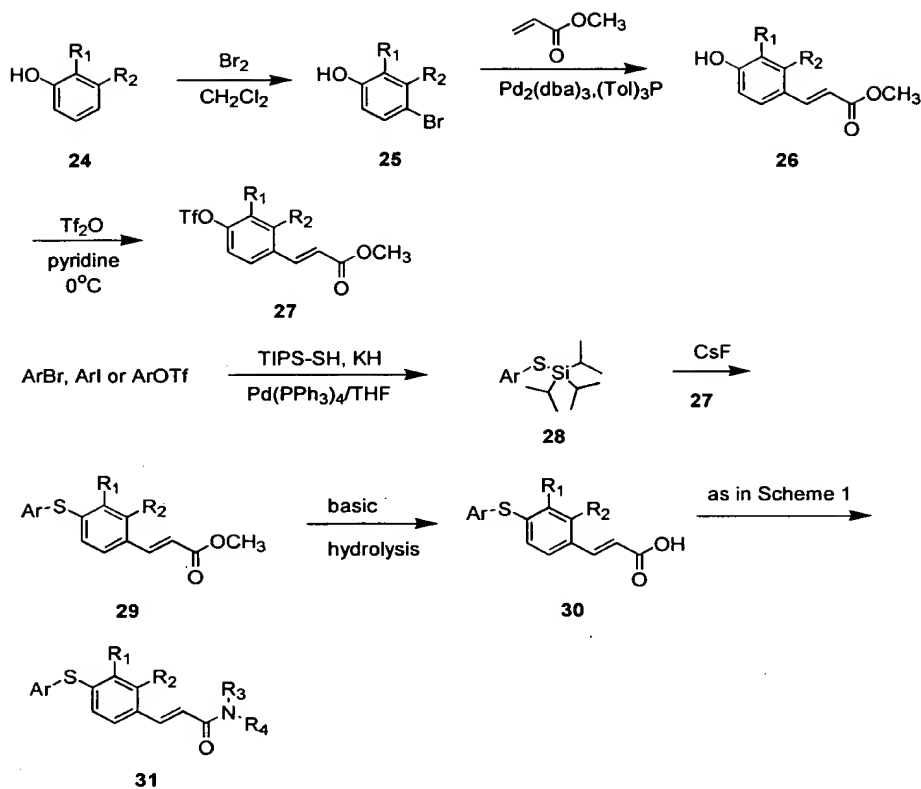
haloarene (e.g. 2,3-dichlorobenzaldehyde, 3-chloro,4-fluorobenzaldehyde or the like) to provide the corresponding product **22**. Alternatively, this same thiolate anion may be coupled with unactivated aryl halides (e.g. aryl bromide or Aryl iodides) using a metal-catalyzed Ullman coupling procedure (for example, using a palladium or nickel catalyst) to give product **23**.

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A further method for producing diarylsulfide cinnamides is shown in Scheme 7, wherein the diaryl sulfide is formed through coupling of a suitably protected aryl thiol **28** to an activated cinnamate ester **27**. Substituted phenol **24** may be brominated to give bromophenol **25**. Heck-type coupling of bromide **25** with an appropriate olefinic substrate, for example methyl acrylate, is effected with palladium catalysis, leading to the cinnamate ester **26**. The phenol is then activated towards further reaction, for example by conversion to the corresponding triflate **27** under standard conditions. The required protected thiol **28** may be prepared by the method of XXX (*Tetrahedron Lett.* **1994**, 35, 3221-3224), by coupling an aryl halide or triflate with triisopropylsilyl thiol under palladium catalysis. The two partners **27** and **28** are then reacted in the presence of a fluoride source, for example cesium fluoride, to provide the diarylsulfide cinnamate **29**. Hydrolysis is accomplished by basic media, such as lithium or sodium hydroxide in water-THF, and the resulting acid **30** is coupled to amines under standard amide-bond forming conditions (for example, EDC/HOBt) to produce the amides **31**.

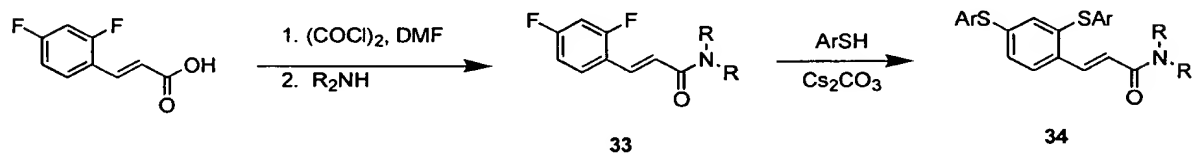
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Scheme 7



A method for preparing cinnamides bearing two arylthio groups is outlined in Scheme 8. Commercially available difluoro cinnamic acid **32** was coupled with an amine, using standard conditions, and this derived amide **33** was reacted with excess aryl thiol to provide the bis-sulfide **34**.

Scheme 8



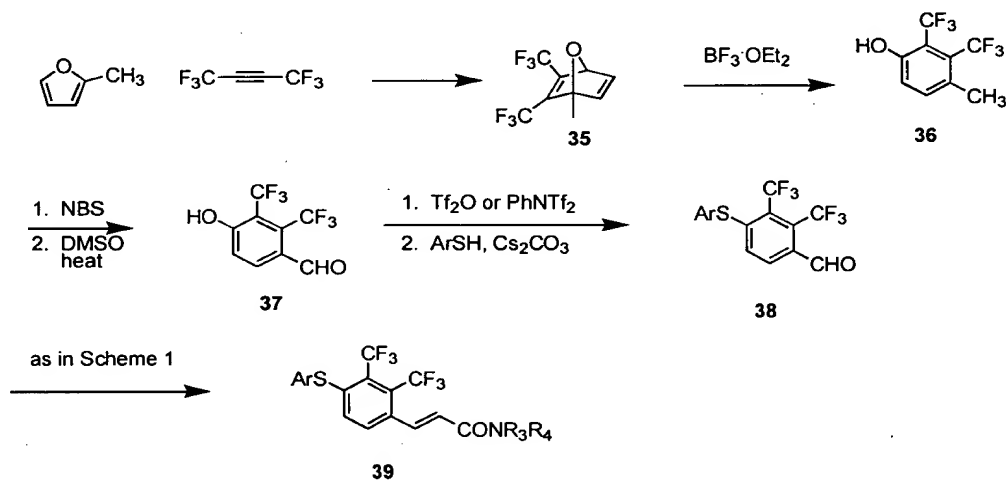
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Compounds which contain trifluoromethyl groups on the cinnamide-portion of inhibitors were made by the method shown in Scheme 9. According to the method of

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XXX (Ref), Diels-Alder reaction between 1,1,1,4,4,4-hexafluoro-2-butyne and 2-methylfuran led to bicyclic ether **35**, which was rearranged with Lewis acid (for example, boron trifluoride etherate) to the phenol **36**. The methyl group is then converted to the corresponding aldehyde **37** by bromination followed by reaction with dimethylsulfoxide. Using the analogous procedures described for Scheme 1 above, the phenol was activated and condensed with thiols under basic conditions to afford diarylsulfide aldehydes **38**, and further converted to cinnamides **39** by the previously described procedures.

Scheme 9

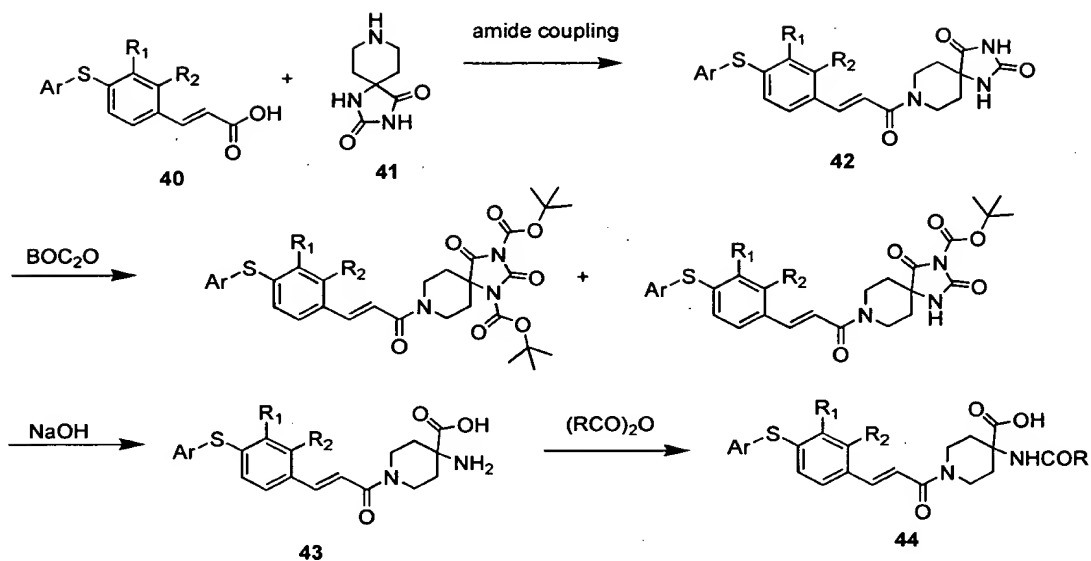


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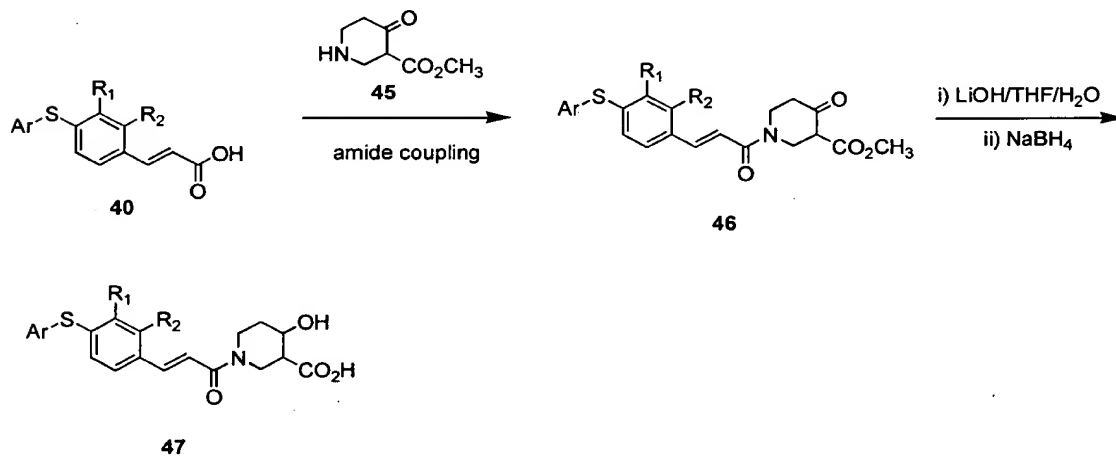
Cinnamides bearing more complex substituted piperidine amides can be produced by the methods outlined in Scheme 10 and 11. Cinnamic acids **40** are coupled to spiro-hydantoin piperidine **41**, and the derived amide **42** is first reacted with an activating reagent (for example di-tert-butyl dicarbonate), and then hydrolyzed to the amino acid **43**. The derived amino group may then be reacted further, for example with acid anhydrides or acid chlorides, to produce amides **44**.

Scheme 10



Further derivatives of piperidine amides can be obtained by coupling of piperidinone **45** with cinnamic acids **40**, as shown in Scheme 11. Standard coupling conditions lead to amide **46**, which is first reduced to the corresponding alcohol, then hydrolyzed to afford hydroxy acid **47**.

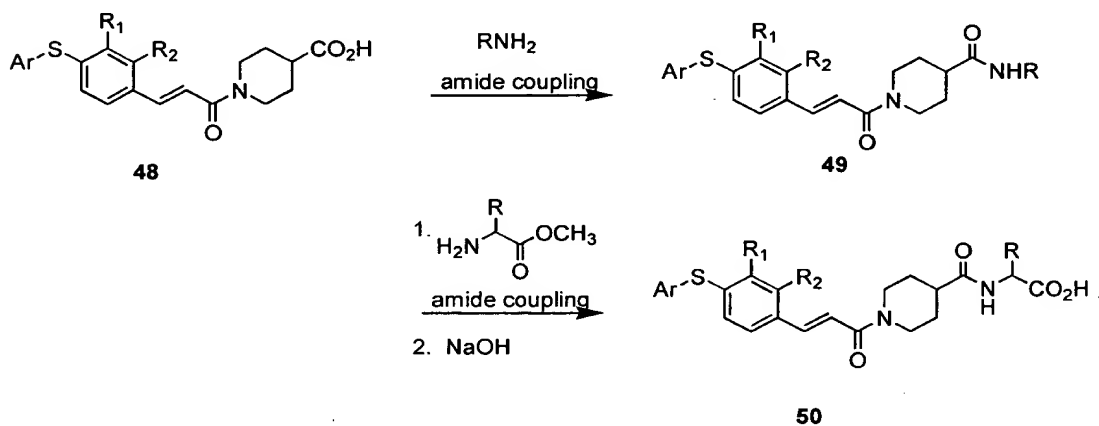
Scheme 11



Also included in this invention are compounds derived from coupling of amines, or amino acid derivatives (such as  $\alpha$ -amino esters) to the carboxylic acid group of cinnamides **48**, using standard coupling and hydrolysis methods, as outlined in Scheme 12. Thus, amides **49** are produced directly from amine coupling reactions.

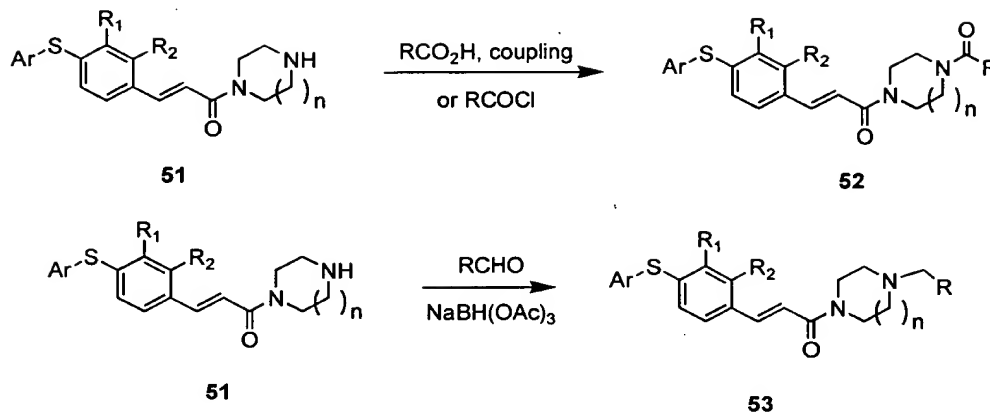
- 5 Amino acid esters are coupled to **48**, and the derived esters are hydrolyzed to the corresponding acids **50**.

Scheme 12



- Inhibitors bearing substituted piperazine (or homopiperazine) cinnamides may
- 10 be produced by the methods described in Scheme 13. The methods described may be utilized to produce piperazine amide **51**. Secondary amine **51** then serves as educt for preparing amides **52**, through standard coupling reactions. Alternatively, **51** may be converted to tertiary amines **53**, through standard reductive alkylation methods (for example, condensation with an aldehyde in the presence of a reducing agent such as
  - 15 sodium triacetoxyborohydride).

Scheme 13

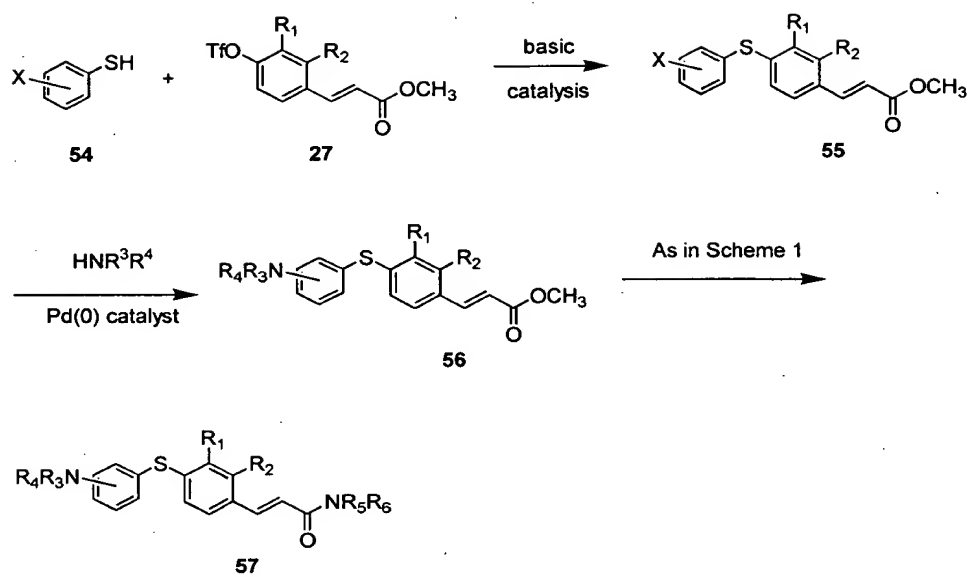


A process for preparing analogs with amino substitutions of the aryl portion of  
 the sulfides is illustrated in Scheme 14. The intermediate triflate **27** is reacted with  
 halo-substituted thiophenols **54** (X = Br, Cl, OTf, OTs) under basic catalysis, to  
 provide the sulfide derivative **55**. The halogen or activated hydroxyl is then  
 substituted with an amine, using the method of Buchwald (Old, D. W.; Wolfe, J. P.;  
 Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723). Similar transition-metal  
 catalyzed reactions may be applied, for example, the method of Hartwig (Hamann, B.  
 C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369-7370). The NR<sub>3</sub>R<sub>4</sub> group may  
 constitute a cyclic or acyclic group, optionally substituted with additional  
 functionalities that may enhance the activities of the compounds, and that further  
 synthetic transformations familiar to those skilled in the art may be applied. For  
 instance, ester groups may be hydrolyzed to the corresponding carboxylic acids or  
 amides. The derived anilino sulfides may then be processed as described above to  
 produce the cinnamides **56**.

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Scheme 14



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Scheme 15 presents a synthesis of a particular class of substituted aniline derivatives bearing a carboxylic acid. A cyclic amino acid **58** may be converted into the corresponding t-butyl ester **61**, through the intermediacy of carbamate **59** and ester **60**, using standard synthetic methods. The amino ester **61** was then reacted with 2-fluoronitrobenzene with mild basic catalysis (for example, cesium fluoride, potassium bicarbonate), to provide the aniline derivative **62**. The nitro group may then be transformed into an iodo-substituted derivative **64**, by first conversion to the aniline **63**, followed by standard diazotization and reaction of the diazonium salt with potassium iodide (among other similar methods for this Sandmeyer reaction). Using the method outlined in Scheme 7, the iodide **64** may be converted to the TIPS-protected arylthiol **65**. In a sequence analogous with that described in Scheme 7, silyl thioether **65** may be reacted with cinnamide triflate **27** in the presence of a fluoride source (for example, cesium fluoride), and thus converted to the diarylsulfide **66**. Standard synthetic transformations (ester hydrolysis, amide coupling, and tert-butyl ester cleavage) provides the desired acid **68**, through intermediate ester **67**.

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Compounds bearing elaborated ether groups on the arylsulfide ring were made according to Scheme 16. Methyl ether cinnamate esters such as **69** were hydrolyzed to the corresponding acids, and then the methyl ether was cleaved with boron tribromide (or alternatively using similar ether cleaving agents, such as trimethylsilyl iodide) to provide the hydroxy acids **70**. Standard coupling methods provided the amides **71**, which were then alkylated on the phenolic group using an appropriate alkyl halide **72** (where L is a linking group consisting of an acyclic or cyclic alkyl, or

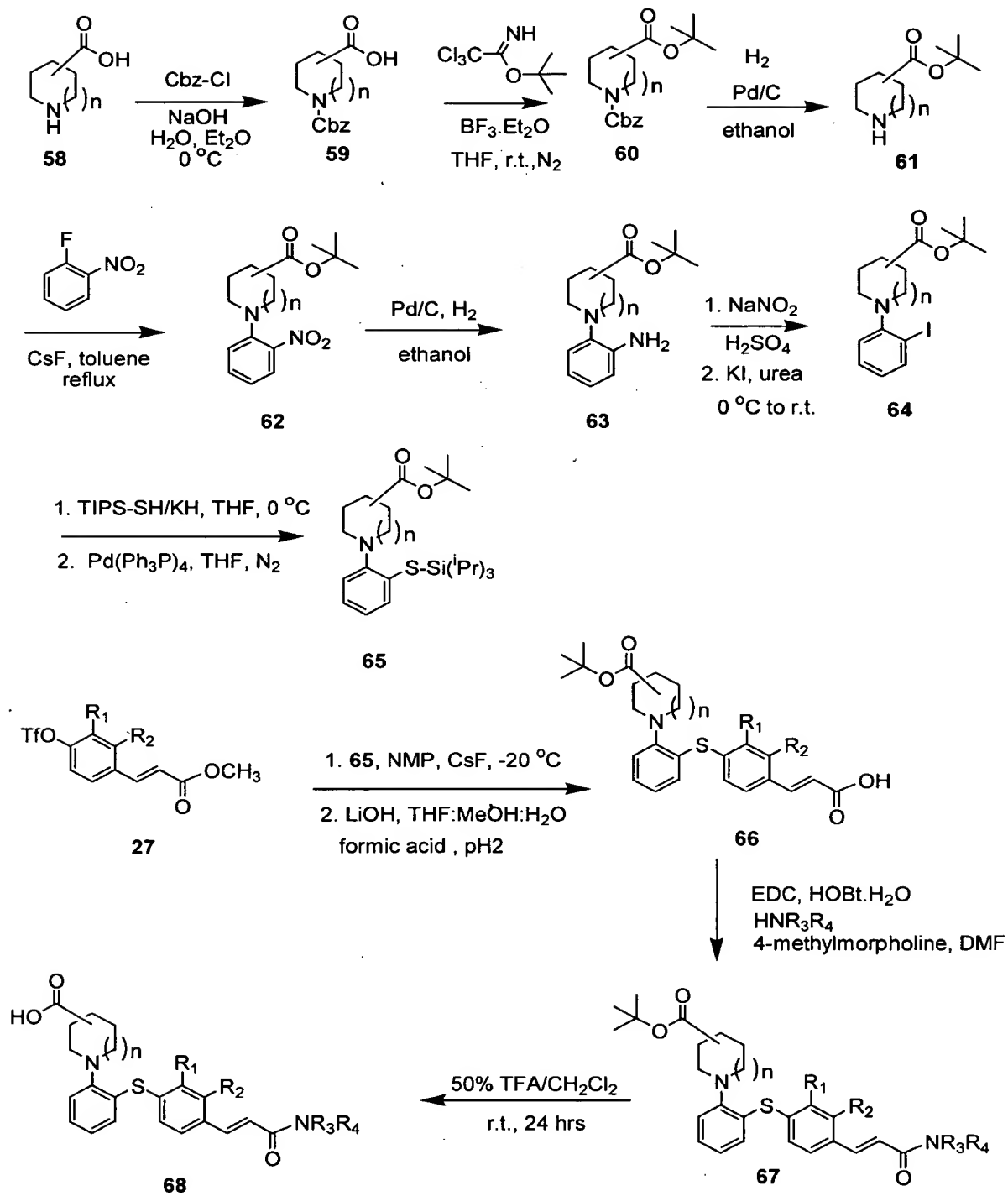
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heterocyclic group) or lactone ( $m=1,2$ ) in the presence of a base (such as potassium *tert*-butoxide, sodium hydride, or cesium carbonate). Alternatively, the phenolic group was alkylated with an ester-bearing alcohol **73**, using Mitsunobu conditions.

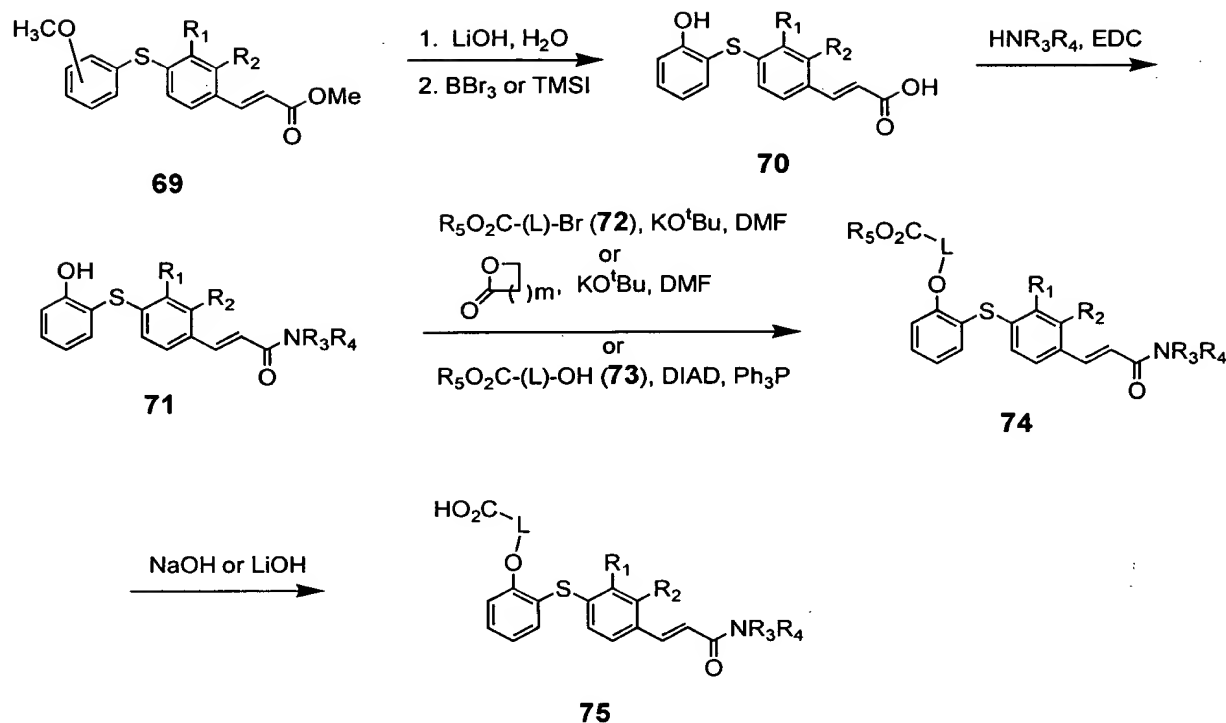
- The resulting ester-bearing ethers **74** were then hydrolyzed to the corresponding acids
- 5 **75** using standard hydrolysis conditions. Alternatively, the ester of **74** may be *tert*-butyl, in which case acidic deprotection to acid **75** would be employed (for example, using trifluoroacetic acid in dichloromethane, or hydrochloric acid in dioxane).

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Scheme 15



Scheme 16



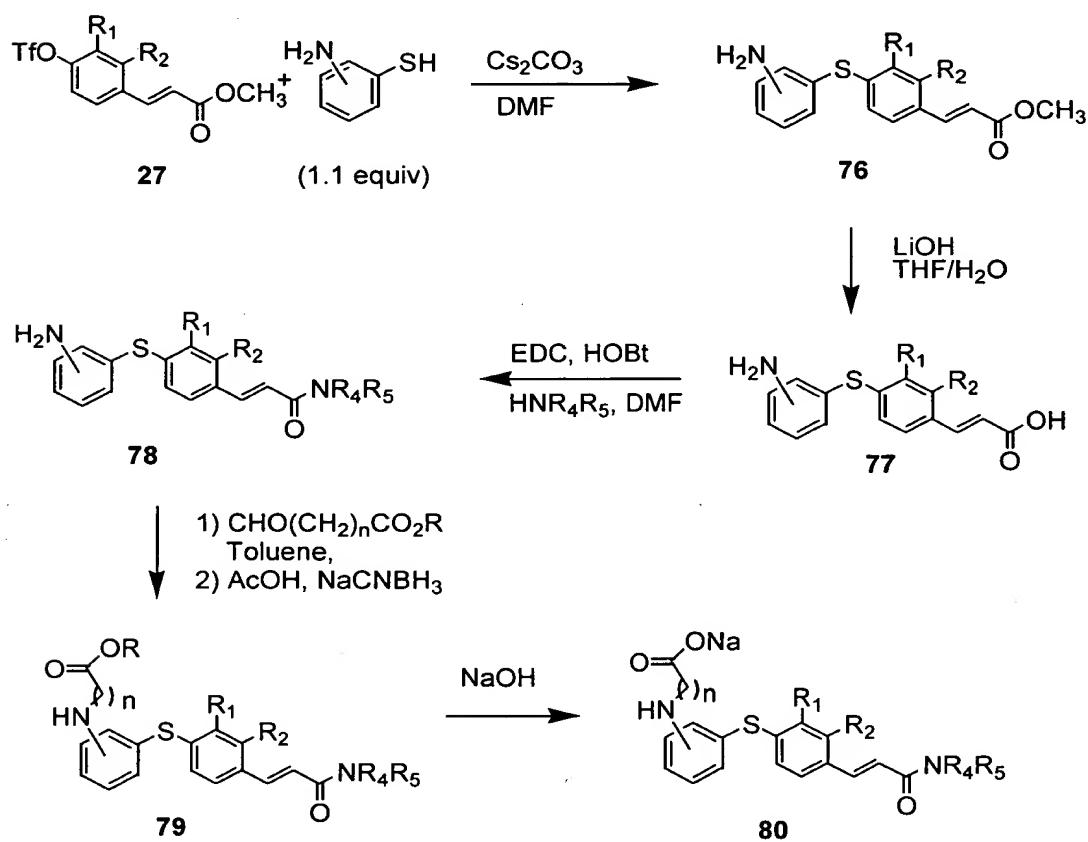
Related compounds bearing elaborated functionalized amino substituents were made according to Scheme 17. Triflate **27** was reacted with an amino thiophenol to produce the diarylsulfide cinnamide **76** in a similar manner to that described in Schemes 1, 2 and 7. The cinnamate ester was hydrolyzed to give acid **77**, which was coupled under standard conditions to provide amide **78**. The amino group of **78** then underwent reductive alkylation with an ester-bearing alkyl aldehyde, using standard conditions (or alternatively using sodium triacetoxyborohydride) to provide the secondary amine **79**. The ester functionality was hydrolyzed to the corresponding acid salt **80**.

An alternative strategy for producing intermediate **78** is shown in Scheme 18. Nitro-substituted *tert*-butyl ester derivative **81** (prepared according to Scheme 14,

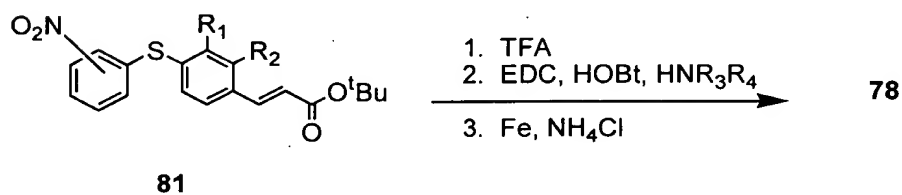
using the tert-butyl analog of cinnamate **27**) was cleaved to the carboxylic acid, converted to the cinnamide using standard conditions, and then the nitro group was reduced using iron powder in aqueous ammonium chloride solution.

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Scheme 17

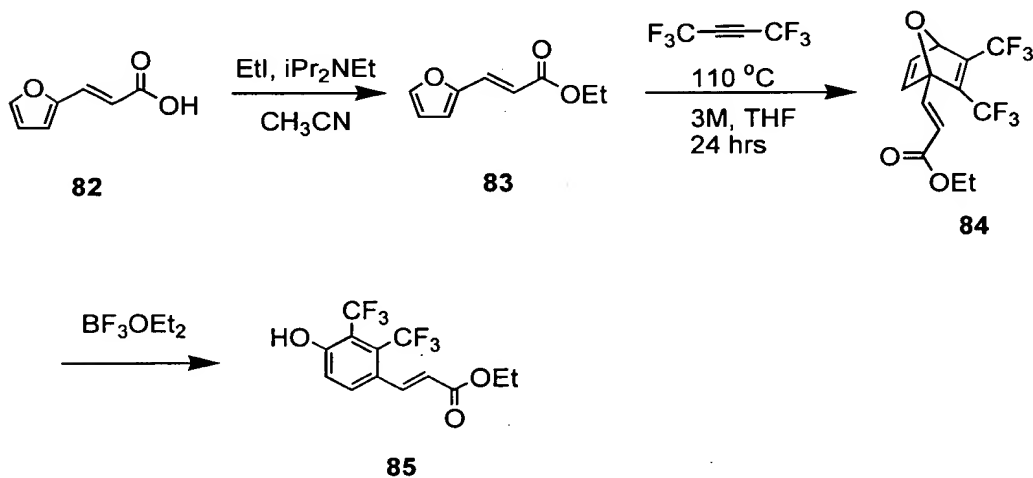


Scheme 18



A modified method for the preparation of analogs bearing 2,3-bis-(trifluoromethyl)cinnamides is illustrated in Scheme 19. Commercially available acrylic acid **82** was esterified with ethyl iodide, and the ester **83** was condensed with 1,1,1,4,4,4-hexafluoro-2-butyne at 110 °C to give the bicyclic adduct **84**. The bicyclic ether was then converted to the corresponding phenol **85** using a Lewis acid (for example boron trifluoride-etherate). Phenol **85** was the utilized as illustrated in Scheme 7 or Scheme 14 to prepare the desired inhibitors.

Scheme 19

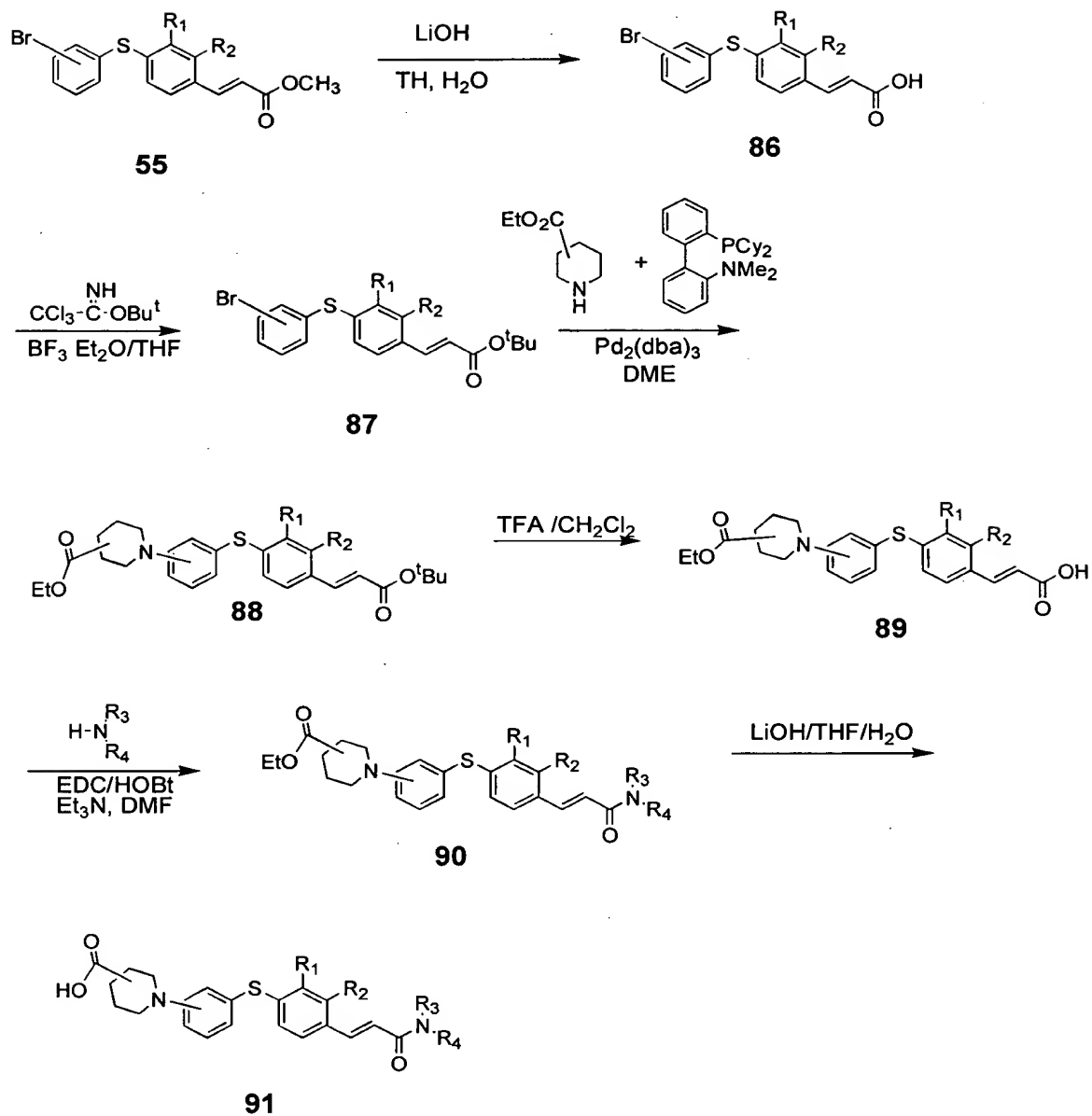


Scheme 20 illustrates an alternative method for preparing substituted anilinosulfides **57**. Cinnamate ester **55** was converted to the corresponding tert-butyl ester **87**, via reaction of acid **86** with tert-butyl trichloroacetimidate under Lewis acid catalysis. The bromide **87** was then coupled with an appropriately functionalized amine (illustrated in Scheme 20 with ethyl pyrrolidinecarboxylates) using palladium

catalysis (for example, using the conditions of Buchwald or Hartwig noted for Scheme 14). The resultant substituted anilines **88** were then first cleaved to acids **89** using acidic conditions (TFA, HCl, or similar known deprotections for tert-butyl esters), then the acids **89** were coupled to amines  $\text{HNR}_3\text{R}_4$  using standard conditions to provide amides **90**. The ethyl ester group of **90** was then hydrolyzed using lithium or sodium hydroxide in aqueous media to produce acids **91**.

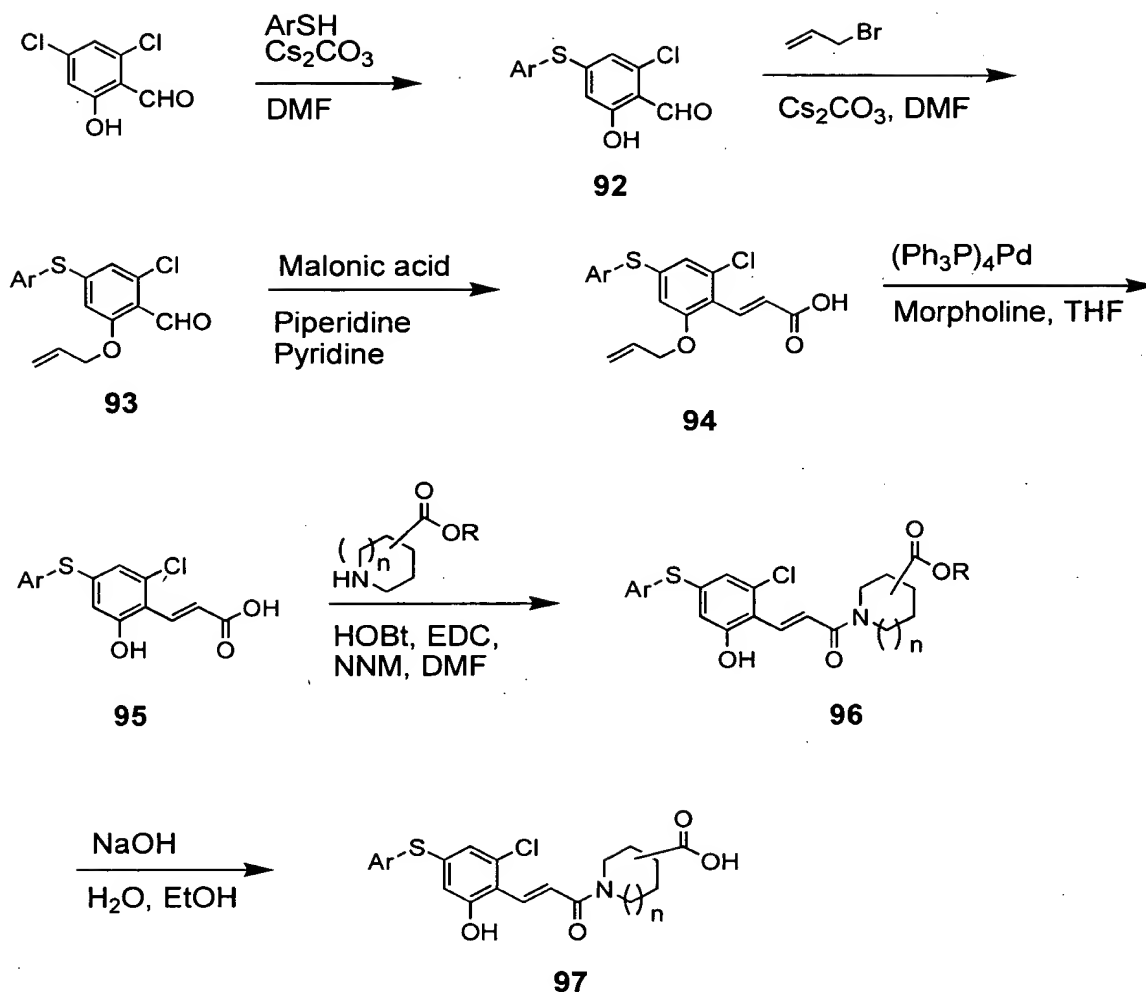
Compounds with a 2,6-disubstitution pattern on the cinnamide ring system were made according to the method of Scheme 21. Commercially available 4,6-dichlorosalicylaldehyde was condensed with arylthiols under basic conditions to provide the diarylsulfide **92**. The phenolic group was protected with allyl bromide, providing the O-allyl derivative **93**. The method outlined in Scheme 1 was used to prepare the corresponding cinnamic acid **94**, then the allyl group was removed using palladium(0)-catalyzed transfer to morpholine, thus producing hydroxy cinnamic acid **95**. The acid group was coupled to a cyclic amino ester ( $n=0, 1, 2$ ;  $\text{R} = \text{Me, Et}$ ) under standard conditions to yield the amide **96**. Basic hydrolysis conditions reveal the acid **97**.

## Scheme 20



90

Scheme 21



### EXAMPLES

The compounds and processes of the present invention may be better understood in connection with the following Examples, which are intended as an illustration of and not a limitation upon the scope of the invention.

#### Example 1

(2,4-Dichlorophenyl)[2-(*E*-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl] sulfide

#### Example 1A

2-[(2,4-Dichlorophenyl)thio]benzaldehyde

To a stirred solution of 2,4-dichlorothiophenol (2.0 g, 11.2 mmol) in 25 mL of anhydrous DMF was added potassium carbonate (3.09 g, 22.4 mmol), followed by 2-chlorobenzaldehyde (1.26 mL, 11.3 mmol). The mixture was then heated under nitrogen atmosphere at 70 °C for 5 hours. The reaction mixture was then allowed to cool to room temperature and partitioned between ether and water. The aqueous layer was extracted with ether once and the combined organic layer was washed with water and brine, dried over sodium sulfate and condensed in vacuo. The crude product was purified via silica gel flash chromatography, eluting with 5-10 % ether/hexanes, to give 2.62 g (9.25 mmol, 83%) of the desired aldehyde as a colorless oil, which solidified slowly upon standing at room temperature.

Example 1B*trans*-2-[(2,4-Dichlorophenyl)thio]cinnamic acid

A mixture of the aldehyde (1.50 g, 5.3 mmol) from Example 1A, malonic acid (1.21 g, 11.6 mmol), piperidine (78.6  $\mu$ L, 0.80 mmol) in 8.0 mL of anhydrous pyridine was heated at 110 °C for 2 hours. Gas evolution ceased during this period. Pyridine was then removed under vacuum. Water and 3N aq. HCl were then added with stirring. The desired cinnamic acid was then collected through filtration, washed with cold water and dried in a vacuum oven overnight to give 1.56 g (4.8 mmol, 91 %) of white solid.

Example 1C(2,4-Dichlorophenyl)[2-(*E*-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl] sulfide

A suspension of the acid (284 mg, 0.87 mmol) from Example 1B in 5 mL of methylene chloride was stirred with (COCl)<sub>2</sub> (84  $\mu$ L, 0.97 mmol), and one drop of DMF under nitrogen atmosphere for 90 minutes. The solvent was then removed under vacuum. The residue (COCl)<sub>2</sub> was removed with benzene (2x) in vacuo. To a separate flask, previously filled with 6-amino-1-hexanol (12 mg, 0.10 mmol), Hunig's base (22.8  $\mu$ L, 0.13 mmol) and DMAP (1.1 mg, 0.008 mmol) in 2.0 mL of CH<sub>2</sub>Cl<sub>2</sub>, the acid chloride (30 mg, 0.087 mmol) in 1.0 mL of CH<sub>2</sub>Cl<sub>2</sub> was then dropped in slowly. After 30 minutes, the reaction mixture was poured into 3N HCl and extracted with ethyl acetate (EtOAc). The organic layer was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, condensed under reduced pressure. The crude product was purified by

preparative TLC to give 21.0 mg (90 %) of the title compound as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.31-1.48 (m, 4H), 1.48-1.70 (m, 4H), 3.37 (q, *J* = 6.7 Hz, 2H), 3.65 (t, *J* = 6.3 Hz, 2H), 5.63 (br s, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.71 (d, *J* = 9.3 Hz, 1H), 7.05 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.31-7.49 (m, 4H), 7.65 (dd, *J* = 2.1, 7.5 Hz, 1H), 7.99 (d, *J* = 15.9 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+NH<sub>4</sub>)<sup>+</sup> at *m/z* 441, 443, 445.

### Example 2

(2,4-Dichlorophenyl)[2-(*E*-((3-(1-imidazolyl)propylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1C substituting 6-amino-1-hexanol with 1-(3-aminopropyl)imidazole. White powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.88 (p, *J* = 7.7 Hz, 2H), 3.11 (q, *J* = 7.7 Hz, 2H), 3.97 (t, *J* = 7.7 Hz, 2H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 0.9 Hz, 1H), 7.17 (d, *J* = 0.9 Hz, 1H), 7.33 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.46-7.65 (m, 4H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.78 (d, *J* = 15.9 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 8.24 (t, *J* = 5.9 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 448, 450, 452. Analysis calculated for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O<sub>1</sub>Cl<sub>2</sub>S<sub>1</sub>·0.87 H<sub>2</sub>O: C, 56.30; H, 4.67; N, 9.38. Found: C, 56.30; H, 4.56; N, 9.27.

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### Example 3

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((2-hydroxyethylamino)carbonyl)ethenyl)phenyl] sulfide

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5 The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with ethanolamine. Colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.57 (q, *J* = 7.65 Hz, 2H), 3.71 (q, *J* = 7.65 Hz, 2H), 6.06 (br s, 1H), 6.40 (d, *J* = 15.3 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.22-7.30 (m, 4H), 7.49-7.60 (m, 1H), 7.55 (d, *J* = 15.3 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 402, 404, 406, 408. Analysis calculated for C<sub>17</sub>H<sub>14</sub>N<sub>1</sub>O<sub>2</sub>Cl<sub>3</sub>S<sub>1</sub>·0.25H<sub>2</sub>O: C, 50.14; H, 3.59; N, 3.44. Found: C, 50.16; H, 3.62; N, 3.29.

10 Example 4

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((6-hydroxyhexylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde. Colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.42 (m, 4H), 1.58 (m, 4H), 3.40 (q, *J* = 6.7 Hz, 2H), 3.65 (br m, 2H), 5.60 (br t, 1H), 6.35 (d, *J* = 15.3 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 7.22-7.30 (m, 4H), 7.49-7.60 (m, 1H), 7.55 (d, *J* = 15.3 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 458, 460, 462, 464. Analysis calculated for C<sub>21</sub>H<sub>22</sub>N<sub>1</sub>O<sub>2</sub>Cl<sub>3</sub>S<sub>1</sub>·0.27H<sub>2</sub>O: C, 54.39; H, 4.90; N, 3.02. Found: C, 54.40; H, 4.85; N, 2.71.

20 Example 5

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((bis-(2-hydroxyethyl)amino)carbonyl)ethenyl) phenyl] sulfide

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A18

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with diethanolamine. Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.99 (br s, 2H), 3.67 (br m, 4H), 3.88 (t,  $J = 5.1$  Hz, 2H), 3.94 (t,  $J = 5.1$  Hz, 2H), 6.94 (d,  $J = 15.3$  Hz, 1H), 6.97 (d,  $J = 8.7$  Hz, 1H), 7.21-7.32 (m, 3H), 7.50-7.54 (m, 1H), 7.58 (d,  $J = 2.4$  Hz, 1H), 7.58 (d,  $J = 15.3$  Hz, 1H). MS (APCI) ( $\text{M} + \text{H}$ ) $^+$  at  $m/z$  446, 448, 450, 452. Analysis calculated for  $\text{C}_{19}\text{H}_{18}\text{N}_1\text{O}_3\text{Cl}_3\text{S}_1 \cdot 1.09\text{H}_2\text{O}$ : C, 48.93; H, 4.36; N, 3.00. Found: C, 48.88; H, 4.00; N, 3.01.

#### Example 6

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-(3-aminopropyl)-2-pyrrolidinone. Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.74 (qu,  $J = 6.0$  Hz, 2H), 2.09 (qu,  $J = 7.5$  Hz, 2H), 2.45 (t,  $J = 8.25$  Hz, 2H), 3.33 (q,  $J = 6.0$  Hz, 2H), 3.42 (q,  $J = 8.25$  Hz, 4H), 6.46 (d,  $J = 15.6$  Hz, 1H), 7.02 (d,  $J = 8.7$  Hz, 1H), 7.14-7.23 (m, 2H), 7.30 (dd,  $J = 2.4, 8.7$  Hz, 1H), 7.51 (d,  $J = 2.4$  Hz, 1H), 7.51 (d,  $J = 15.6$  Hz, 1H), 7.60 (d,  $J = 2.1$  Hz, 1H). MS (DCI/ $\text{NH}_3$ ) ( $\text{M} + \text{H}$ ) $^+$  at  $m/z$  483, 485, 487, 489. Analysis calculated for  $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_2\text{Cl}_3\text{S}_1 \cdot 0.57\text{H}_2\text{O}$ : C, 53.48; H, 4.52; N, 5.67. Found: C, 53.49; H, 4.60; N, 5.65.

Example 7

(2,4-Dichlorophenyl)[2-chloro-4-( E-((1-morpholinyl)carbonyl)ethenyl)phenyl]

sulfide

Sub  
A18

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.59-3.80 (m, 8H), 6.83 (d, *J* = 15.6 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 7.16-7.32 (m, 3H), 7.49-7.53 (m, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 15.6 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 428, 430, 432, 434. Analysis calculated for C<sub>19</sub>H<sub>16</sub>N<sub>1</sub>O<sub>2</sub>Cl<sub>3</sub>S<sub>1</sub>·0.46H<sub>2</sub>O: C, 52.22; H, 3.90; N, 3.20. Found: C, 52.20; H, 3.76; N, 3.12.

Example 8

(2,4-Dichlorophenyl)[2-chloro-4-( E-((4-methylpiperazin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-methylpiperazine. Colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.37 (s, 3H), 2.51 (br m, 4H), 3.63-3.87 (br m, 4H), 6.85 (d, *J* = 15.6 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 7.19-7.25 (m, 2H), 7.27 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.52 (t, *J* = 0.9 Hz, 1H), 7.57 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 441, 443, 445, 447. Analysis calculated for C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>O<sub>1</sub>Cl<sub>3</sub>S<sub>1</sub>·0.45H<sub>2</sub>O: C, 53.39; H, 4.46; N, 6.23. Found: C, 53.37; H, 4.46; N, 6.07.

Example 9

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

5 The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-acetylpiperazine. White solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.15 (s, 3H), 3.50-3.58 (m, 2H), 3.58-3.85 (m, 6H), 6.85 (d, *J* = 15.3 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.24-7.36 (m, 3H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 15.3 Hz, 1H),  
10 7.61 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 486, 488, 490, 492. Analysis calculated for C<sub>21</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>3</sub>S<sub>1</sub>·0.85H<sub>2</sub>O: C, 51.99; H, 4.30; N, 5.77. Found: C, 52.03; H, 4.27; N, 5.67.

Example 10

15 (2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-(2-pyridyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-(2-pyridyl)piperazine. White solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ  
20 3.59 (br m, 2H), 3.69 (br m, 2H), 3.78 (br m, 2H), 3.86 (br m, 2H), 6.64-6.72 (m, 2H), 6.90 (d, *J* = 15.6 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.22-7.25 (m, 2H), 7.31 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.49-7.57 (m, 2H), 7.61 (d, *J* = 15.6 Hz, 1H), 7.62 (d, *J* = 2.4 Hz,

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A18

1H), 8.19-8.24 (m, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 504, 506, 508, 510. Analysis calculated for C<sub>24</sub>H<sub>20</sub>N<sub>3</sub>O<sub>1</sub>Cl<sub>3</sub>S<sub>1</sub>: C, 57.10; H, 3.99; N, 8.32. Found: C, 57.12; H, 4.06; N, 8.29.

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Example 11

(2-(Hydroxymethyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

00000"5674550

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-mercaptobenzyl alcohol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with morpholine. White solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.50-3.62 (br m, 6H), 3.65-3.74 (br m, 2H), 4.54 (d, *J* = 5.7 Hz, 2H), 5.33 (t, *J* = 5.7 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 7.28 (d, *J* = 15.0 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 15.0 Hz, 1H), 7.43 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.50 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.55 (dd, *J* = 2.1, 7.8 Hz, 1H), 7.68 (dd, *J* = 1.5, 8.1 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 390, 392. Analysis calculated for C<sub>20</sub>H<sub>20</sub>N<sub>1</sub>O<sub>3</sub>Cl<sub>1</sub>S<sub>1</sub> · 0.09H<sub>2</sub>O: C, 61.35; H, 5.20; N, 3.58. Found: C, 61.37; H, 5.48; N, 3.81.

20

Example 12

(2-Bromophenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde

5

[illegible]

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## 20

20

ethenyl)phenyl] sulfide

Sub  
A18

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 1-[2-(2-hydroxyethoxy)ethyl]piperazine. Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.73 (br m, 6H), 3.58-3.68 (m, 2H), 3.68-4.00 (m, 8H), 6.84 (d,  $J$  = 15.3 Hz, 1H), 6.97 (d,  $J$  = 8.7 Hz, 1H), 7.20-7.34 (m, 3H), 7.54 (d,  $J$  = 7.5 Hz, 1H), 7.58 (d,  $J$  = 15.3 Hz, 1H), 7.58-7.65 (overlapping d, 1H). MS (DCI/ $\text{NH}_3$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  515, 517, 519, 521.

#### Example 15

10 (2-Bromophenyl)[2-chloro-4-(*E*-((3-(hydroxymethyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 3-hydroxymethylpiperidine.  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 300MHz)  $\delta$  8.07 (d,  $J$  = 17.7 Hz, 1H), 7.80 (d,  $J$  = 7.7 Hz, 1H), 7.63 (br d,  $J$  = 7.7 Hz, 1H), 7.44 (d,  $J$  = 7.0 Hz, 1H), 7.40 (br s, 2H), 7.35 (m, 1H), 7.25 (dd 7.7, 1.5, 1H), 7.06 (dd,  $J$  = 8.1, 2.9, 1H), 4.57 (m, 1H), 4.45 (m, 1H), 4.16 (br m, 2H), 1.2 – 1.8 (m, 8H). HRMS calculated for  $\text{C}_{21}\text{H}_{21}\text{N}_1\text{O}_2\text{S}_1\text{Br}_1\text{Cl}_1$ : 466.0243. Observed: 466.0247.

#### Example 16

20 (2-Bromophenyl)[2-chloro-4-(*E*-((2-(hydroxymethyl)piperidin-1-yl)carbonyl)

00544795.033100

ethenyl)phenyl] sulfide

Sub  
A18

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 2-

5 hydroxymethylpiperidine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.03 (m, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.61 (m, 1H), 7.30 – 7.45 (m, 4H), 7.23 (m, 1H), 7.07 (m, 1H), 4.79 (m, 2H), 4.61 (m, 2H), 4.10 (m, 1H), 1.50 (m, 6H). HRMS calculated for C<sub>21</sub>H<sub>21</sub>N<sub>1</sub>O<sub>2</sub>S<sub>1</sub>Br<sub>1</sub>Cl<sub>1</sub>: 466.0243. Observed: 466.0247.

Example 17

10 (2-Bromophenyl)[2-chloro-4-( E-((3-acetamidopyrrolidin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 3-

15 acetamidopyrrolidine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.14 (m, 1H), 8.07 (dd, J = 9.8, 1.7 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.64 (dd, J = 8.1, 1.7 Hz, 1H), 7.25 – 7.47 (m, 4H), 7.10 (t, J = 7.8 Hz, 1H), 7.03 (dd, J = 8.1, 1.7 Hz, 1H), 3.45 – 4.34 (m, 6H), 2.02 (m, 2H), 1.81 (ap d, J = 1.4 Hz, 1H). HRMS calculated for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>Br<sub>1</sub>Cl<sub>1</sub>:

20 479.0196. Observed: 479.0183.

Example 18

00544795.033100

(2-Bromophenyl)[2-chloro-4-( E-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Sub  
A18

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-hydroxypiperidine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.08 (d, J = 1.7 Hz, 1H), 7.80 (dd, J = 8.0, 1.5 Hz, 1H), 7.63 (dd, J = 8.3, 1.9 Hz, 1H), 7.44 (ap dd, J = 7.5, 1.4 Hz, 2H), 7.40 (ap d, J = 3.7 Hz, 2H), 7.34 (dt, J = 7.6, 1.8 Hz, 1H), 7.25 (dd, J = 7.5, 1.7 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 4.76 (br s, 1H), 4.01 (m, 2H), 3.72 (m, 1H), 3.12 (m, 1H), 1.75 (m, 2H), 1.32 (m, 2H). HRMS calculated for C<sub>20</sub>H<sub>19</sub>N<sub>1</sub>O<sub>2</sub>S<sub>1</sub>Br<sub>1</sub>Cl<sub>1</sub>: 452.0087. Observed: 452.0076.

Example 19

(2-Bromophenyl)[2-chloro-4-( E-((piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with piperidine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.08 (d, J = 1.7 Hz, 1H), 7.80 (dd, J = 8.1, 1.4 Hz, 1H), 7.63 (dd, J = 8.1, 1.7 Hz, 1H), 7.44 (ap dd, J = 7.6, 1.5 Hz, 1H), 7.39 (ap d, J = 4.8 Hz, 2H), 7.34 (dt, J = 7.5, 1.6, 1H), 7.24 (dd, J = 7.5, 1.7, 1H), 7.05 (d, J = 8.1 Hz, 1H), 3.65 (br m, 2H), 3.53 (br m, 2H), 1.62 (br m, 2H), 1.50 (br m, 4H). HRMS calculated for C<sub>20</sub>H<sub>19</sub>N<sub>1</sub>O<sub>1</sub>S<sub>1</sub>Br<sub>1</sub>Cl<sub>1</sub>: 436.0130. Observed: 436.0122.

00541795.033100

Example 20

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

5

The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with nipecotic acid. Colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.44-1.68 (br m, 1H), 1.68-2.00 (br m, 2H), 2.51-2.67 (br m, 1H), 3.13-3.37 (br m, 1H), 3.80-4.12 (br m, 1H), 4.30-5.00 (br m, 3H), 6.86 (d, *J* = 15.3 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 7.16-7.24 (m, 2H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.47-7.55 (m, 1H), 7.55 (d, *J* = 15.3 Hz, 1H), 7.60 (br d, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 470, 472, 474, 476.

10

Example 21

(2,4-Dichlorophenyl)[2-chloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

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The title compound was prepared by the procedures described in Example 1 substituting 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with isonipecotic acid. Colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.68-1.85 (m, 2H), 1.98-2.09 (m, 2H), 2.60-2.72 (m, 1H), 2.90-3.13 (br m, 1H), 3.17-3.38 (br m, 1H), 3.93-4.12 (br m, 1H), 4.38-4.59 (br m, 1H), 6.86 (d, *J* = 15.3 Hz, 1H), 6.99 (dd, *J* = 8.7 Hz, 1H), 7.20-7.25 (m, 2H), 7.28 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.49-7.53

20

Sub  
A14

007E0" 56ZTH560

Sub  
Aix

(m, 1H), 7.56 (d,  $J = 15.3$  Hz, 1H), 7.60 (d,  $J = 1.8$  Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at  $m/z$  470, 472, 474, 476.

### Example 22

5      (2-Bromophenyl)[2-chloro-4-(*E*-((4-acetylhomopiperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

007EE0"56ZT4560

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-acetylhomopiperazine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.10 (m, 1H), 7.81 (d,  $J = 7.7$  Hz, 1H), 7.64 (m, 1H), 7.24 – 7.51 (m, 5H), 7.05 (m, 1H), 3.39 – 3.77 (m, 8H), 1.97 (m, 3H), 1.68 (m, 2H). HRMS calculated for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>S<sub>1</sub>Br<sub>1</sub>Cl<sub>1</sub>: 493.0352. Observed: 493.0352.

10

### 15      Example 23

(2-Bromophenyl)[2-chloro-4-(*E*-((thiomorpholin-1-yl)carbonyl)ethenyl)phenyl]  
sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with thiomorpholine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.10 (d,  $J = 1.5$  Hz, 1H), 7.80 (d,  $J = 8.5$  Hz, 1H), 7.64 (dd,  $J = 8.1, 1.5$  Hz, 1H), 7.31 – 7.48 (m, 4H), 7.36 (m, 1H), 7.26 (dd,  $J = 8.1, 1.8$  Hz,

20

Sub  
A18

1H), 7.05 (d  $J = 8.1$  Hz, 1H), 3.96 (m, 2H), 3.82 (m, 2H), 2.62 (m, 4H). HRMS calculated for  $C_{19}H_{17}N_1O_1S_2Br_1Cl_1$ : 455.9681. Observed: 455.9676.

#### Example 24

5 (2-Bromophenyl)[2-chloro-4-(*E*-((4-(1-benzimidazol-2-onyl)piperidin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

00100"56714560

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with 4-(1-benzimidazol-  
10 2-onyl)piperidine.  $^1H$  NMR (DMSO- $d_6$ , 300MHz)  $\delta$  8.14 (d,  $J = 1.5$  Hz, 1H), 7.80 (dd,  $J = 7.9, 1.3$  Hz, 1H), 7.67 (dd,  $J = 8.1, 1.8$  Hz, 1H), 7.48 (ap s, 2H), 7.44 (dt,  $J = 7.5, 1.2$ , 1H), 7.34 (dt,  $J = 7.6, 1.6$ , 1H), 7.26 (dd,  $J = 7.7, 1.8$  Hz, 1H), 7.22 (m, 1H), 7.06 (d,  $J = 8.1$ , 1H), 6.97 (ap d,  $J = 2.6$ , 3H), 4.64 (m, 1H), 4.48 (m, 2H), 2.79 (m, 2H), 2.29 (m, 2H), 1.78 (m, 2H). HRMS calculated for  $C_{27}H_{23}N_3O_2S_1Br_1Cl_1$ :  
15 568.0461. Observed: 568.0477.

#### Example 25

(2-Bromophenyl)[2-chloro-4-(*E*-((2-tetrahydroisoquinoliny)carbonyl)  
ethenyl)phenyl] sulfide

20 The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3-chloro-4-fluoro-benzaldehyde, and 6-amino-1-hexanol with

Sub  
A18

tetrahydroisoquinoline.  $^1\text{H}$  NMR (DMSO- $d_6$ , 300MHz)  $\delta$  8.12 (d,  $J$  = 7.4 Hz, 1H), 7.81 (dd,  $J$  = 7.7, 1.1 Hz, 1H), 7.67 (dd,  $J$  = 8.3, 1.3 Hz, 1H), 7.47 (m, 2H), 7.43 (dd,  $J$  = 7.5, 1.3 Hz, 2H), 7.34 (dt,  $J$  = 7.6, 1.7 Hz, 1H), 7.27 (d 7.7 Hz, 1H), 7.19 (m, 4H), 7.05 (d,  $J$  = 8.1 Hz, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 3.95 (t,  $J$  = 5.9 Hz, 1H), 3.78 (t,  $J$  = 5.7 Hz, 1H), 2.89 (t,  $J$  = 5.3 Hz, 1H), 2.83 (t,  $J$  = 3.7, 1H). HRMS calculated for  $\text{C}_{24}\text{H}_{19}\text{N}_1\text{O}_2\text{S}_1\text{Br}_1\text{Cl}_1$ : 484.0138. Observed: 484.0128.

#### Example 26

10 (2-Methylphenyl)[2-trifluoromethyl-4-( E-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with 1-acetylpiperazine.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$  7.79 (s, 1H); 7.63 (d,  $J$  = 15.4Hz, 1H); 7.51 (d,  $J$  = 6.8 Hz, 1H); 7.41-7.33 (m, 3H); 7.28 (m, 1H); 6.83 (d,  $J$  = 15.4 Hz, 1H); 6.79 (d,  $J$  = 6.8 Hz, 1H); 3.80-3.60 (m, 6H); 3.57-3.50 (m, 2H); 2.34 (s, 3H); 2.14 (s, 3H). MS (ESI)  $m/z$  919 (2M+Na) $^+$ , 897 (2M+H) $^+$ , 471 (M+Na) $^+$ , 449 (M+H) $^+$ .

#### Example 27

20 (2-Methylphenyl)[2-trifluoromethyl-4-( E-((1-morpholinyl)carbonyl)  
ethenyl)phenyl] sulfide

Sub  
A18

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with morpholine. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 7.79 (s, 1H); 7.63 (d, J = 14.0 Hz, 1H); 7.52 (d, J = 7.6 Hz, 1H); 7.40-7.30 (m, 3H); 7.28 (m, 1H); 6.87 (d, J = 14.0 Hz, 1H); 6.84 (d, J = 7.6 Hz, 1H); 3.73 (br s, 8H); 2.34 (s, 3H). MS (ESI) *m/z* 837 (2M+Na)<sup>+</sup>, 815 (2M+H)<sup>+</sup>, 408 (M+H)<sup>+</sup>.

#### Example 28

10 (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((2-(1-morpholinyl)ethylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with 2-(1-morpholinyl)ethylamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 7.80 (s, 1H); 7.56 (d, J = 15.8 Hz, 1H); 7.50 (d, J = 8.1 Hz, 1H); 7.40-7.32 (m, 3H); 7.28 (m, 1H); 6.79 (d, J = 15.8 Hz, 1H); 6.40 (d, J = 8.1 Hz, 1H); 3.75 (t, J = 4.6 Hz, 4H); 3.51 (q, J = 5.5 Hz, 2H), 2.57 (t, J = 5.8 Hz, 2H); 2.55-2.48 (m, 4H); 2.34 (s, 3H). MS (ESI) *m/z* 923 (2M+Na)<sup>+</sup>, 473 (M+Na)<sup>+</sup>, 451 (M+H)<sup>+</sup>.

#### Example 29

20 (2-Methylphenyl)[2-trifluoromethyl-4-(*E*-((4-phenylpiperazin-1-yl)carbonyl)

ethenyl)phenyl] sulfide

Sub A18  
The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with 4-phenylpiperazine. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 7.81 (s, 1H); 7.64 (d, J = 16.0 Hz, 1H); 7.51 (d, J = 8.2 Hz, 1H); 7.40-7.27 (m, 6H); 6.98-6.90 (m, 4H); 6.80 (d, J = 8.2 Hz, 1H); 3.88 (br s, 4H); 2.23 (br s, 4H); 2.34 (s, 3H). MS (ESI) *m/z* 987 (2M+Na)<sup>+</sup>, 965 (2M+H)<sup>+</sup>, 505 (M+Na)<sup>+</sup>, 483 (M+H)<sup>+</sup>, 451.

Example 30

(2-Methylphenyl)[2-trifluoromethyl-4-( E-((3-(1-pyrrolidin-2-  
only)propylamino)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with 1-pyrrolidin-2-only)propylamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 7.78 (s, 1H); 7.53 (d, J = 15.6 Hz, 1H); 7.49 (d, J = 7.2 Hz, 1H); 7.40-7.33 (m, 3H); 7.14 (m, 1H); 6.80 (d, J = 8.2 Hz, 1H); 6.43 (d, J = 15.6 Hz, 1H); 3.41 (m, 4H); 3.32 (q, J = 6.1 Hz, 2H); 2.43 (t, J = 6.6 Hz, 2H); 2.34 (s, 3H), 2.08 (m, 2H), 1.75 (m, 2H). MS (ESI) *m/z* 947 (2M+Na)<sup>+</sup>, 925 (2M+H)<sup>+</sup>, 485 (M+Na)<sup>+</sup>, 463 (M+H)<sup>+</sup>.

Example 31

(2-Methylphenyl)[2-trifluoromethyl-4-( E-((cyclopropylamino)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1

5 substituting 2,4-dichlorothiophenol with 2-methylthiophenol, 2-chlorobenzaldehyde  
with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with  
cyclopropylamine. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 7.76 (s, 1H); 7.56 (d, J = 15.4 Hz,  
1H); 7.50 (d, J = 8.4 Hz, 1H); 7.40-7.30 (m, 3H); 7.28 (m, 1H); 6.88 (d, J = 8.4 Hz,  
1H); 6.30 (d, J = 15.4 Hz, 1H); 5.70 (br s, 1H), 2.95 (m, 1H); 2.34 (s, 3H); 0.85 (m,  
10 2H); 0.57 (m, 2H). MS (ESI) *m/z* 777 (2M+Na)<sup>+</sup>, 755 (2M+H)<sup>+</sup>, 400 (M+Na)<sup>+</sup>, 378  
(M+H)<sup>+</sup>.

Example 32

(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

15

Example 32A

1-Chloro-2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) benzene

To a stirred solution of *trans*-4-chloro-3-nitrocinnamic acid (1.50 g, 6.59 mmol)  
20 and 1-acetylpiperazine (0.89 g, 6.94 mmol) in 20 mL of DMF at room temperature  
was added EDAC (1.4 g, 7.30 mmol). The mixture was then stirred at room  
temperature for 2 hours. TLC indicated the complete consumption of the acid. Water

00760" 562F4560

Sub  
A19

Sub  
A 18

was then added to quench the reaction and to precipitate out the product. Cinnamide was then collected through filtration and washed with cold water. The light yellow product was dried in vacuum oven overnight at 40 °C to give 2.04 g (6.03 mmol, 91.6 %) of the title compound.

5

Example 32B

(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

NOTE: 56274560

To a stirred solution of 4-chloro-3-nitro-cinnamide (275 mg, 0.814 mmol) from Example 32A in 1.0 mL of DMF was added potassium carbonate (169 mg, 1.22 mmol), followed by the dropwise addition of 2,4-dichlorothiophenol (146 mg, 0.815 mmol). The mixture was then stirred at room temperature for 60 minutes. Completion of the reaction was indicated by the TLC. Water was then added to precipitate the product. Filtration, washing with cold water, and drying in a vacuum oven afforded 350 mg (0.728 mmol, 89%) of the titled compound as light yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.05 (s, 3H), 3.42-3.50 (br m, 4H), 3.50-3.64 (br m, 2H), 3.64-3.79 (br m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 15.3 Hz, 1H), 7.55 (d, *J* = 15.3 Hz, 1H), 7.63 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 497, 499, 501. Analysis calculated for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub> Cl<sub>2</sub> S<sub>1</sub>·0.82H<sub>2</sub>O: C, 50.94; H, 4.20; N, 8.49. Found: C, 50.91; H, 4.21; N, 8.69.

10

15

20

Example 33

Sub  
A18

(2,4-Dichlorophenyl)[2-nitro-4-( E-((3-(1-pyrrolidin-2-onyl)propylamino)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 1-acetylpiperazine with 1-(3-aminopropyl)-2-pyrrolidinone. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.64 (p, *J* = 7.1 Hz, 2H), 1.91 (p, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 8.3 Hz, 2H), 3.15 (q, *J* = 6.3 Hz, 2H), 3.21 (dd, *J* = 9.9, 17.7 Hz, 2H), 3.32 (overlapping t, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 15.6 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 2.4, 8.1 Hz, 1H), 7.79 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 8.18 (t, *J* = 6.0 Hz, 1H), 8.46 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 494, 496.

Example 34

(2,3-Dichlorophenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)

15

ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32B substituting 2,4-dichlorothiophenol with 2,3-dichlorothiophenol. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.42-3.50 (br m, 4H), 3.50-3.64 (br m, 2H), 3.64-3.79 (br m, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 15.6 Hz, 1H), 7.55 (t, *J* = 7.65 Hz, 1H), 7.57 (d, *J* = 15.6 Hz, 1H), 7.78 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.87 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.95 (dd, *J* = 2.7, 9.0 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 497, 499, 501.

Example 35

(4-Bromophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]  
sulfide

5       The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 4-bromothiophenol. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 3.74 (br m, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 15.0 Hz, 1H), 7.54 (d, *J* = 15.0 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 9.0 Hz, 2H),  
10   7.92 (dd, *J* = 2.1, 9.0 Hz, 1H), 8.65 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 507, 509.

Example 36

(4-Methylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]

15       sulfide

      The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with *p*-thiocresol. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 2.39 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.68 (br m, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H),  
20   7.39 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 15.0 Hz, 1H), 7.53 (d, *J* = 15.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.89 (dd, *J* = 2.1, 8.7 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+NH<sub>4</sub>)<sup>+</sup> at *m/z* 443.

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Example 37

(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(tert-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

5           The title compound was prepared by the procedures described in Example 32 substituting 1-acetylpiperazine with *tert*-butyl piperazine carboxylate. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.42 (s, 9H), 3.36 (overlapping m, 4H), 3.55 (br m, 2H), 3.70 (br m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.92 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 538, 540, 542.

Example 38

(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(2-furoylcarbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

15

Example 38A

(2,4-Dichlorophenyl)[2-nitro-4-( E-((piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide  
Trifluoroacetic Acid Salt

20           The compound (100 mg, 0.186 mmol) from Example 37 was dissolved in 0.5 mL of neat trifluoroacetic acid (TFA). The mixture was stirred at room temperature

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for 1 hour. The TFA was then removed under vacuum to give the title compound (105 mg) as a yellow solid.

### Example 38B

5 (2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(2-furoylcarbonyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

To a stirred solution of piperazine TFA salt (35 mg, 0.067 mmol) from

Example 38A In 2.0 mL of  $\text{CH}_2\text{Cl}_2$  was added  $\text{Et}_3\text{N}$  (23  $\mu\text{L}$ , 0.17 mmol), 4-dimethylaminopyridine (DMAP) (1.0 mg, 0.0082 mmol), and furyl chloride (8.0  $\mu\text{L}$ , 0.080 mmol). The mixture was then stirred at room temperature for 30 minutes before the solvent was removed. The crude product was purified with Gilson HPLC system, YMC C-18 column, 75x30 mm I.D., S-5  $\mu\text{M}$ , 120 Å, and a flow rate of 25 mL/min,  $\lambda=214, 245$  nm; mobile phase A, 0.05 M  $\text{NH}_4\text{OAc}$ , and B,  $\text{CH}_3\text{CN}$ ; linear gradient 20-100% of B in 20 minutes to give the title compound (24 mg, 67%) as light-yellow powder;  $^1\text{H}$  NMR ( $d^6$ -DMSO, 300 MHz)  $\delta$  3.62-3.87 (br m, 8H), 6.66 (q,  $J = 2.1$  Hz, 1H), 6.84 (d,  $J = 8.7$  Hz, 1H), 7.04 (d,  $J = 3.3$  Hz, 1H), 7.44 (d,  $J = 15.3$  Hz, 1H), 7.56 (d,  $J = 15.3$  Hz, 1H), 7.63 (dd,  $J = 2.4, 8.1$  Hz, 1H), 7.83 (d,  $J = 8.4$  Hz, 1H), 7.87 (d,  $J = 2.1$  Hz, 1H), 7.92 (dd,  $J = 2.1, 12.0$  Hz, 1H), 7.96 (d,  $J = 2.1$  Hz, 1H), 8.70 (d,  $J = 2.1$  Hz, 1H). MS (APCI)  $(\text{M}+\text{H})^+$  at  $m/z$  532, 534, 536.

20

### Example 39

(2,4-Dichlorophenyl)[2-nitro-4-( *E*-((4-(methanesulfonyl)piperazin-1-yl)carbonyl)

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(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(diethylaminocarbonyl)piperazin-1-yl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting furoyl chloride with *N,N*-diethylcarbamyl chloride. Light-yellow powder;

5 <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.06 (t, *J* = 6.9 Hz, 6H), 3.12 (br m, 4H), 3.15 (q, *J* = 6.9 Hz, 4H), 3.58 (br m, 2H), 3.72 (br m, 2H), 6.83 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.92 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.95 (d, *J* = 2.7 Hz, 1H), 8.68 (d, *J* = 2.1 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 537, 539, 541.

10

Example 42

(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(*tert*-butoxycarbonylmethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting CH<sub>2</sub>CL<sub>2</sub> with CH<sub>3</sub>CN as solvent, and furoyl chloride with *tert*-butyl

15 bromoacetate. Light-yellow powder; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.47 (s, 9H), 2.70 (br m, 4H), 3.21 (s, 2H), 3.74 (br m, 2H), 3.82 (br m, 2H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 15.0 Hz, 1H), 7.39 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 15.0 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 8.43 (br d, 20 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 552, 554, 556.

Example 43

(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(carboxycarbonyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

Example 43A

5 (2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(carbethoxycarbonyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 38B substituting furoyl chloride with ethyl oxalyl chloride.

10

Example 43B

(2,4-Dichlorophenyl)[2-nitro-4-( E-((4-(carboxycarbonyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

To a stirred solution of the ethyl ester (40 mg, 0.074 mmol) from Example 43A in 2 mL of ethanol was added saturated LiOH (0.25 mL). The mixture was then stirred at room temperature for 2 hours. Water (2 mL) was then added to the reaction mixture, which was then acidified to pH = 2 with concentrated HCl. The precipitates were collected through filtration, washed with cold water, dried under vacuum to give the titled compound (30 mg, 79%) as light yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 3.52 (br m, 4H), 3.62 (br m, 2H), 3.76 (br m, 2H), 6.84 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 15.3 Hz, 1H), 7.56 (d, J = 15.3 Hz, 1H), 7.63 (dd, J = 2.7, 8.7 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 2.7 Hz, 1H), 8.70 (br d, 1H). MS (APCI) (M-COO)<sup>+</sup> at m/z 466, 468, 470.

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A20

Example 44

(2,4-Dichlorophenyl)[2-nitro-4-(*E*-((4-(carboxymethyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

5

The title compound was prepared by the procedures described in Example 38A substituting compound from Example 37 with compound from Example 42. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 3.14 (s, 2H), 3.40 (overlapping br m, 4H), 3.44 (br m, 1H), 3.51 (br m, 1H), 3.57 (br m, 1H), 3.71 (br m, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.52 (d, *J* = 15.6 Hz, 1H), 7.63 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.92 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 8.68 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 496, 498, 500.

Example 45

(2-Methylphenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with *o*-thiocresol. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.03 (s, 3H), 2.29 (s, 3H), 3.47 (br m, 4H), 3.53 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.83 (br m, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 15.0 Hz, 1H), 7.36-7.42 (m, 1H), 7.46-7.57 (m, 3H), 7.63 (d, *J* = 6.9 Hz, 1H), 7.89 (dd, *J* = 2.4, 9.0 Hz, 1H), 8.66 (d, *J* = 2.4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 426.

**sulfide**

10

(2-Aminophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]

## 15

20

1H), 7.89 (dd,  $J = 1.8, 8.7$  Hz, 1H), 8.64 (d,  $J = 1.8$  Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at  $m/z$  427.

#### Example 48

5      (2-Hydroxymethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-mercaptobenzyl alcohol. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz)  $\delta$  2.03 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 10      1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.73 (br m, 1H), 4.53 (d,  $J = 5.7$  Hz, 1H), 5.34 (t,  $J = 5.7$  Hz, 1H), 6.65 (d,  $J = 8.7$  Hz, 1H), 7.40 (d,  $J = 15.3$  Hz, 1H), 7.46 (d,  $J = 7.8$  Hz, 1H), 7.53 (d,  $J = 15.3$  Hz, 1H), 7.59 (d,  $J = 7.5$  Hz, 1H), 7.64 (d,  $J = 7.5$  Hz, 1H), 7.87 (dd,  $J = 2.1, 8.7$  Hz, 1H), 8.65 (d,  $J = 2.1$  Hz, 1H). MS (APCI) (M+NH<sub>4</sub>)<sup>+</sup> at  $m/z$  459.

15

#### Example 49

(2-Ethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-ethylthiophenol. Light-yellow powder; <sup>1</sup>H 20      NMR (d<sup>6</sup>-DMSO, 300 MHz)  $\delta$  1.01 (t,  $J = 7.65$  Hz, 3H), 2.04 (s, 3H), 2.69 (q,  $J = 7.65$  Hz, 2H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.59 (br m, 1H), 3.67 (br m, 1H), 3.73

(br m, 1H), 6.64 (d,  $J = 8.7$  Hz, 1H), 7.38 (dd,  $J = 2.4, 7.5$  Hz, 1H), 7.40 (d,  $J = 15.6$  Hz, 1H), 7.50-7.61 (m, 3H), 7.53 (d,  $J = 15.6$  Hz, 1H), 7.89 (dd,  $J = 2.4, 8.7$  Hz, 1H), 8.64 (d,  $J = 2.4$  Hz, 1H). MS (APCI) (M+Cl)<sup>-</sup> at  $m/z$  474, 476.

5

Example 50

(2-iso-Propylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-isopropylthiophenol. Light-yellow powder;

10 <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.05 (d,  $J = 6.9$  Hz, 6H), 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.72 (br m, 1H), 6.64 (d,  $J = 8.4$  Hz, 1H), 7.34-7.41 (m, 2H), 7.39 (d,  $J = 15.3$  Hz, 1H), 7.52 (d,  $J = 15.3$  Hz, 1H), 7.56-7.73 (m, 2H), 7.90 (dd,  $J = 2.1, 8.7$  Hz, 1H), 8.64 (d,  $J = 2.1$  Hz, 1H). MS (APCI) (M+NH<sub>4</sub>)<sup>+</sup> at  $m/z$  471. Analysis calculated for C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub> S<sub>1</sub>·0.21H<sub>2</sub>O: C, 63.03; H, 5.96; N, 9.13. Found: C, 63.03; H, 6.04; N, 9.19.

15

Example 51

(2-tert-Butylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl)phenyl] sulfide

20 The title compound was prepared by the procedures described in Example 32 substituting 2,4-dichlorothiophenol with 2-*tert*-butylthiophenol. Light-yellow powder; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.46 (s, 9H), 2.04 (s, 3H), 3.47 (br m, 4H), 3.52 (br

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m, 1H), 3.60 (br m, 1H), 3.67 (br m, 1H), 3.73 (br m, 1H), 6.68 (d,  $J = 8.7$  Hz, 1H), 7.35 (t,  $J = 7.5$  Hz, 1H), 7.39 (d,  $J = 15.3$  Hz, 1H), 7.45-7.57 (m, 2H), 7.50 (d,  $J = 15.3$  Hz, 1H), 7.65 (d,  $J = 8.1$  Hz, 1H), 7.88 (dd,  $J = 2.4, 8.7$  Hz, 1H), 8.64 (d,  $J = 2.4$  Hz, 1H). MS (APCI) ( $M + NH_4$ )<sup>+</sup> at  $m/z$  485.

5

### Example 52

(2-Chlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl))  
2-propenyl)phenyl] sulfide

10

### Example 52A

3'-Chloro-4'-[(2-chlorophenyl)thio]acetophenone

The title compound was prepared by the procedures described in Example 1A substituting 2,4-dichlorothiophenol with 2-chlorothiophenol, and 2-chlorobenzaldehyde with 4'-fluoro-3'-chloroacetophenone.

15

### Example 52B

(2-Chlorophenyl)[2-chloro-4-(*E*-(1-ethoxycarbonyl) 2-propenyl)phenyl] sulfide

To a stirred suspension of NaH (60% in mineral oil, 121 mg, 3.03 mmol) in 20 mL of anhydrous THF under nitrogen atmosphere was added triethyl phosphonoacetate dropwise. After 20 minutes, the acetophenone (600 mg, 2.02 mmol) from Example 52A in THF (5 mL) was added in one portion. The resulting clear solution was then stirred at room temperature for 7 hours. Reaction was then stopped, most of the solvent was evaporated, and the residue was partitioned between

EtOAc (2x20 mL) and water. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The crude product was purified using silica gel flash column chromatography eluting with 5-10% Et<sub>2</sub>O in hexanes to give the (*E*)-isomer of the cinnamate (500 mg, 68%) as a white solid.

5

### Example 52C

(2-Chlorophenyl)[2-chloro-4-(*E*-(1-carboxy) 2-propenyl)phenyl] sulfide

Sub  
A2:  
A mixture of the cinnamate (500 mg, 1.37 mmol) from Example 52B in 5 mL of EtOH/THF (4:1) was stirred with sat. LiOH solution (0.50 mL) at 50 °C for 2 hours. The mixture was then acidified with 3N HCl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL). The combined organic layer was dried over MgSO<sub>4</sub>, concentrated under reduced pressure to give the titled compound (450mg, 97%) as a white solid.

### Example 52D

15 (2-Chlorophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl))  
2-propenyl)phenyl] sulfide

The title compound was prepared using the cinnamic acid from Example 52C by the procedures described in Example 1C substituting 6-amino-1-hexanol with 1-acetylpiperazine. White solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.10-2.20 (m, 3H), 2.25 (s, 3H), 3.40-3.80 (m, 8H), 6.28 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 7.19-7.36 (m, 4H), 7.46-7.56 (m, 2H). MS (APCI) (M+NH<sub>4</sub>)<sup>+</sup> at *m/z* 466, 468, 470.

20

Example 53

(2-(1-Morpholinylmethyl)phenyl)[2-chloro-4-( E-((1-morpholinyl)carbonyl)  
ethenyl) phenyl] sulfide

5

Example 53A

(2-(1-Bromomethyl)phenyl)[2-chloro-4-( E-((1-morpholinyl)carbonyl)  
ethenyl) phenyl] sulfide

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To a stirred solution of benzyl alcohol (195 mg, 0.32 mmol) from Example 11  
in 2.0 mL of anhydrous DMF was added LiBr (48 mg, 0.35 mmol). The mixture was  
10 then cooled in an ice-water bath, and PBr<sub>3</sub> (60 µL, 0.40 mmol) was dropped in slowly.  
The ice bath was then removed and the mixture was stirred at room temperature for 1  
hour. Water was then added, the mixture was then partitioned between EtOAc and  
aqueous NaHCO<sub>3</sub>. The aqueous layer was extracted with EtOAc once. The combined  
organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated on a  
15 rotavap. The crude bromide (230mg) was used directly for the alkylation without  
purification.

Example 53B

(2-(1-Morpholinylmethyl)phenyl)[2-chloro-4-( E-((1-morpholinyl)carbonyl)  
ethenyl) phenyl] sulfide

20

Sub  
A22  
To a stirred solution of morpholine (10 µL, 0.11 mmol) in 0.5 mL of CH<sub>3</sub>CN  
was added Hunig's base (23.7 µL, 0.14 mmol), followed by the bromide (40 mg,

Sub  
A22

0.091 mmol). The mixture was then stirred at room temperature for 2 hours. Solvent was then removed and the crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.33 (br t, 4H), 3.45 (br t, 4H), 3.50-3.65 (m, 6H), 3.56 (s, 2H), 3.65-3.80 (br m, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 15.3 Hz, 1H), 7.35-7.41 (m, 2H), 7.43 (d, *J* = 15.3 Hz, 1H), 7.46 (td, *J* = 2.4, 8.1 Hz, 1H), 7.52 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 459, 461.

10

Example 54

(2-(4-(1,3-Benzodioxolyl-5-methyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-(1-morpholinyl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared by the procedures described in Example 53B substituting morpholine with 1-piperonylpiperazine. White solid; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.13-2.40 (br m, 8H), 3.28 (s, 2H), 3.49-3.64 (br m, 6H), 3.54 (s, 2H), 3.70 (br m, 2H), 5.97 (s, 2H), 6.69 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.79 (d, *J* = 1.8 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 15.3 Hz, 1H), 7.33-7.38 (m, 2H), 7.38-7.50 (m, 2H), 7.43 (d, *J* = 15.3 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 592, 594.

20

Example 55

(2-(4-(*iso*-Propylaminocarbonylmethyl)piperazin-1-ylmethyl)phenyl)[2-chloro-4-(*E*-  
((1-  
morpholinyl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 53B  
5 substituting morpholine with *N*-isopropyl-1-piperazineacetamide. White solid; <sup>1</sup>H  
NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.04 (d, *J* = 6.3 Hz, 6H), 2.20-2.42 (br m, 8H), 2.78 (s,  
2H), 3.47-3.64 (br m, 6H), 3.56 (s, 2H), 3.64-3.76 (br m, 2H), 3.85 (qd, *J* = 6.3, 8.1  
Hz, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 15.6 Hz, 1H), 7.31-7.39 (m, 2H), 7.43  
(d, *J* = 15.6 Hz, 1H), 7.45 (td, *J* = 2.7, 6.3 Hz, 1H), 7.50 (dd, *J* = 2.1, 8.7 Hz, 1H),  
10 7.55 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 557,  
559.

#### Example 56

(2-((*N*-Ethoxycarbonylmethyl-*N*-methyl)aminomethyl)phenyl)[2-chloro-4-(*E*-((1-  
15 morpholinyl)carbonyl) ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 53B  
substituting morpholine with ethyl sarcosinate hydrochloride. White solid; <sup>1</sup>H NMR  
(d<sup>6</sup>-DMSO, 300 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 2H), 3.30 (s, 2H), 3.51-3.66  
(br m, 6H), 3.66-3.75 (br m, 2H), 3.78 (s, 2H), 4.05 (q, *J* = 7.2 Hz, 2H), 6.75 (d, *J* =  
20 8.7 Hz, 1H), 7.30 (d, *J* = 15.3 Hz, 1H), 7.33-7.38 (m, 2H), 7.42-7.50 (m, 2H), 7.43 (d,  
*J* = 15.3 Hz, 1H), 7.53 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* =  
2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 489, 491.

00760" 56/4560

Example 57

(2-Formylphenyl)[2-chloro-4-( E-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

Sub  
A23

To a stirred solution of the alcohol (368 mg, 0.94 mmol) from Example 11 in 5 mL of anhydrous acetonitrile was added activated 4Å molecular sieves, TPAP (3.3 mg, 0.0094 mmol), and NMO (110 mg, 1.03 mmol). The mixture was then stirred at room temperature for 3 hours. The reaction mixture was then quenched with dimethyl sulfide (100 µL). The crude product was filtered through celite, washed with acetonitrile, condensed in vacuo. The titled compound was purified by silica gel 10 column chromatography to give a white solid (216 mg, 59 %). <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 3.60 (br m, 6H), 3.73 (br m, 2H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 15.3 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 15.3 Hz, 1H), 7.52 (td, *J* = 1.8, 8.1 Hz, 1H), 7.61 (td, *J* = 1.8, 8.1 Hz, 1H), 7.71 (dd, *J* = 2.1, 8.4 Hz, 1H), 8.02 (dd, *J* = 2.1, 8.4 Hz, 1H), 8.14 (d, *J* = 2.1 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 388, 390.

15

Example 58

(2-(4-Formylpiperazin-1-ylmethyl)phenyl)[2-chloro-4-( E-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 53B 20 substituting morpholine with 1-formyl piperazine. White solid; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.20-2.32 (m, 6H), 2.74 (br m, 2H), 3.48 (s, 2H), 3.59 (m, 6H), 3.70 (br m, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 15.6 Hz, 1H), 7.35-7.41 (m, 2H), 7.42

(d,  $J = 15.6$  Hz, 1H), 7.45-7.52 (m, 3H), 7.98 (d,  $J = 2.1$ , 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at  $m/z$  486, 488.

### Example 59

5     (2-(*E*-((1-Morpholinyl)carbonyl)ethenyl)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

NOTE: 562F1560  
Sub  
A24

A mixture of bromide (80 mg, 0.18 mmol) from Example 12, acryloylmorpholine (33 mg, 0.23 mmol), Pd(OAc)<sub>2</sub> (2.0 mg, 0.009 mmol), P(*o*-tolyl)<sub>3</sub> (17 mg, 0.056 mmol), Et<sub>3</sub>N (39 μL, 0.27 mmol), and anhydrous DMF (1.0 mL) in a pressure tube was flushed with nitrogen for 5 minutes before it capped and heated at 110 °C over night. TLC indicated almost complete consumption of the starting bromide. The reaction mixture was then allowed to cool down to room temperature, partitioned between EtOAc and water. The aqueous layer was extracted once with EtOAc. The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, condensed under reduced pressure. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a light-brown solid (35 mg, 39%). <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 3.43-3.88 (m, 16H), 6.58 (d,  $J = 8.7$  Hz, 1H), 7.30 (d,  $J = 15.3$  Hz, 2H), 7.43 (d,  $J = 15.3$  Hz, 1H), 7.47-7.64 (m, 4H), 7.86 (d,  $J = 15.3$  Hz, 1H), 8.06 (d,  $J = 2.1$  Hz, 1H), 8.14 (d,  $J = 7.5$  Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+NH<sub>4</sub>)<sup>+</sup> at  $m/z$  516, 518. Analysis calculated for

5 (2-Formylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]  
sulfide

15

**(2-Formylphenyl)[2-chloro-4-( *E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide,**

A mixture of the aldehyde (20 mg, 0.052 mmol) from Example 57, 1,1-dimethyl hydrazine (3.9  $\mu$ L, 0.052 mmol) in 0.5 mL of EtOH with a tiny amount of AcOH was stirred at room temperature over night. The solvent was then removed and the product was purified by preparative TLC to give the titled compound (20 mg,

Sub  
A25

130

90%) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.91 (s, 6H), 3.55-3.82 (br m, 8H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.76 (d, *J* = 15.3 Hz, 1H), 7.05 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.26 (td, *J* = 1.8, 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.47-7.57 (m, 2H), 7.54 (m, 2H), 8.04 (dd, *J* = 1.8, 8.7 Hz, 1H). MS (DCI/NH<sub>3</sub>) (M+H)<sup>+</sup> at *m/z* 430, 432, 434, 436.

Example 62

(2-((3-(1-Morpholinyl)propyl)-1-amino)phenyl)[2-chloro-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

A mixture of bromide (60 mg, 0.14 mmol) from Example 12, aminopropylmorpholine (24 μL, 0.17 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (1.2 mg, 0.0013 mmol), BINAP (2.5 mg, 0.004 mmol), NaOt-Bu (19 mg, 0.20 mmol), 18-crown-6 (50 mg, 0.20 mmol), and anhydrous toluene (1 mL) in a pressure tube was flushed with nitrogen for 3 minutes before it was capped and heated at 80 °C over night. The reaction was then stopped, and allowed to cool down to room temperature. The reaction mixture was partitioned between EtOAc and water, and the aqueous layer was extracted once with EtOAc. The combined organic layer was then washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, condensed under reduced pressure. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a light-brown oil (30 mg, 44%). <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.62 (quintet, *J* = 6.5 Hz, 2H), 2.15-2.26 (m, 8H), 3.17 (q, *J* = 6.5 Hz, 2H), 3.22-3.76 (m, 12 H), 3.50 (t, *J* = 6.5 Hz, 2H), 5.72 (t, *J* = 5.7 Hz, 1H), 6.47 (d, *J*

Sub  
A24  
= 8.7 Hz, 1H), 6.68 (t,  $J = 7.2$  Hz, 1H), 6.81 (d,  $J = 8.4$  Hz, 1H), 7.26 (d,  $J = 15.6$  Hz, 1H), 7.35-7.42 (m, 2H), 7.43 (d,  $J = 15.6$  Hz, 1H), 7.44 (d,  $J = 8.4$  Hz, 1H), 7.49 (d,  $J = 8.4$  Hz, 1H), 8.00 (d,  $J = 2.1$  Hz, 1H). MS (APCI) ( $M+H$ )<sup>+</sup> at  $m/z$  502, 504.

5

Example 63

(2,4-Dichlorophenyl)[2-bromo-4-(*E*-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)  
ethenyl)phenyl] sulfide

Example 63A

10

(2,4-Dichlorophenyl)[2-amino-4-(*E*-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)  
ethenyl)phenyl] sulfide

15

A mixture of nitro compound (780 mg, 1.58 mmol) from Example 33, SnCl<sub>2</sub> (1.50 g, 7.91 mmol) in 25 mL of anhydrous EtOH was refluxed under nitrogen atmosphere for 90 minutes. The reaction was then allowed to cool down to room temperature, quenched with sat. NaHCO<sub>3</sub>, extracted with EtOAc (2x50 mL). The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, condensed in vacuo to give the crude aniline as yellowish brown solid, which was converted to the bromide without purification.

20

Example 63B

(2,4-Dichlorophenyl)[2-bromo-4-(*E*-((3-(1-pyrrolidin-2-yl)propylamino)carbonyl)  
ethenyl)phenyl] sulfide

0044795.033100  
0044795.033100

132

Sub  
A26

To a stirred solution of *t*-butyl nitrite (57  $\mu$ L, 0.48 mmol), CuBr<sub>2</sub> (87 mg, 0.39 mmol) in 2.0 mL of CH<sub>3</sub>CN at room temperature was added a solution of aniline from Example 63A (150 mg, 0.323 mmol) in 1.0 mL of CH<sub>3</sub>CN. The dark green solution was then heated at 65 °C under nitrogen atmosphere for 90 minutes. The reaction mixture was then allowed to cool down to room temperature, partitioned between EtOAc and 3N HCl. The organic layer was then washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, condensed in vacuo. The crude product was then purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a light-brown solid (50 mg, 29%). Colorless oil; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz)  $\delta$  1.63 (quintet, *J* = 7.2 Hz, 2H), 1.91 (quintet, *J* = 8.4 Hz, 2H), 2.22 (t, *J* = 8.4 Hz, 2H), 3.09-3.47 (m, 6H), 6.67 (d, *J* = 15.3 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.38 (d, *J* = 15.3 Hz, 1H), 7.50 (dd, *J* = 2.4, 8.7 Hz, 1H), 7.57 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.86 (d, *J* = 2.4 Hz, 1H), 7.96 (d, *J* = 2.1 Hz, 1H), 8.13 (t, *J* = 6.0 Hz, 1H). MS (ESI) (M+H)<sup>+</sup> at *m/z* 527, 529, 531, 533.

15

Example 64

(2,4-Dichlorophenyl)[2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl]  
sulfide

20

Example 64A

[1-Fluoro-2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl) benzene]

The title compound was prepared by the procedures described in Example 59

Example 64B

5 (2,4-Dichlorophenyl)[2-formyl-4-(*E*-((1-morpholinyl)carbonyl)ethenyl)phenyl]  
sulfide

The title compound was prepared by the procedures described in Example 32 substituting 4-chloro-3-nitro-cinnamide with the compound from Example 64A.

White solid;  $^1\text{H}$  NMR ( $d^6$ -DMSO, 300 MHz)  $\delta$  3.60 (br m, 6H), 3.71 (br m, 2H), 6.82 (d,  $J = 8.7$  Hz, 1H), 7.35 (d,  $J = 15.6$  Hz, 1H), 7.54 (d,  $J = 15.6$  Hz, 1H), 7.55 (dd,  $J = 2.4, 8.7$  Hz, 1H), 7.61 (d,  $J = 8.7$  Hz, 1H), 7.86 (dd,  $J = 2.4, 8.4$  Hz, 1H), 7.91 (d,  $J = 2.4$  Hz, 1H), 8.41 (d,  $J = 2.1$  Hz, 1H), 10.19 (s, 1H). MS (DCI/ $\text{NH}_3$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  422, 424, 426, 428.

15 Example 65

(2-Chloro-6-formylphenyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

### Example 65A

20 (2-Carbomethoxyethyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with methyl 3-mercaptopropionate, and 6-amino-1-hexanol with 1-acetyl piperazine.

Example 65B

5      (2-Chloro-6-formylphenyl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

00100 552450  
Sub  
A27  
To a stirred solution of the compound (105 mg, 0.26 mmol) from Example 65A in 2 mL of THF under nitrogen atmosphere at 0 °C was added *t*-BuOK solution (1.0M, 281 µL, 0.29 mmol). Light orange precipitates appeared immediately. After  
10 completion of the addition, the reaction mixture was stirred at room temperature for 1 hour before the solvent was removed on a rotavap under reduced pressure.

The yellow thiolate thus obtained was dissolved in 0.5 mL of DMF, and 2,3-dichlorobenzaldehyde was then added. The mixture was then heated at 80 °C under nitrogen for 2 hours. Reaction was then stopped and the solvent was removed under  
15 vacuum. The crude product was purified with Gilson Preparative HPLC as described in Example 38B to give the titled compound as a white solid (25 mg, 21%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.05 (s, 3H), 3.48-3.58 (m, 2H), 3.58-3.84 (m, 6H), 6.53 (d, *J* = 8.7 Hz, 1H), 6.80 (d, *J* = 15.3 Hz, 1H), 7.19 (dd, *J* = 1.8, 8.7 Hz, 1H), 7.51-7.62 (m, 2H), 7.60 (d, *J* = 15.3 Hz, 1H), 7.84 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.99 (dd, *J* = 1.8, 8.4  
20 Hz, 1H). MS (APCI) (M+NH<sub>4</sub>)<sup>+</sup> at *m/z* 480, 482, 484.

Example 66

(2-Cyanophenyl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 65B substituting 2,3-dichlorobenzaldehyde with 2-fluorobenzonitrile, giving a white solid.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.15 (s, 3H), 3.48-3.57 (m, 2H), 3.59-3.84 (m, 6H),  
6.86 (d, J = 15.6 Hz, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.41 (d, J  
= 6.6 Hz, 1H), 7.46 (dd, J = 1.8, 8.4 Hz, 1H), 7.55 (dd, J = 1.8, 8.1 Hz, 1H), 7.61 (d, J  
= 15.6 Hz, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.75 (dd, J = 1.8, 8.4 Hz, 1H). MS  
(DCI/NH<sub>3</sub>) (M+NH<sub>4</sub>)<sup>+</sup> at *m/z* 443.

10

Example 67

(2-Isopropylphenyl)[2-cyano-4-( E-((morpholin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

15

Example 67A

(2-Isopropylphenyl)(4-bromo-2-cyanophenyl)sulfide

The title compound was prepared by the procedures described in Example 1A substituting 2,4-dichlorothiophenol with isopropylthiophenol, and 2-chlorobenzaldehyde with 2-fluorobenzonitrile.

20

Example 67B

(2-Isopropylphenyl)[2-cyano-4-( E-((morpholin-1-yl)carbonyl)

ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 59 substituting the bromide from Example 12 with the bromide from Example 67A, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.19 (d, *J* = 6.9 Hz, 6H), 3.49 (septet, *J* = 6.9 Hz, 1H), 3.58-3.87 (m, 8H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 15.6 Hz, 1H), 7.20-7.30 (m, 1H), 7.42 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.46 (d, *J* = 3.0 Hz, 2H), 7.49 (dd, *J* = 1.8, 6.9 Hz, 1H), 7.57 (d, *J* = 15.6 Hz, 1H), 7.76 (d, *J* = 1.8 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 393.

Example 68(2-Bromophenyl)[2-nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 32B substituting 2,4-dichlorothiophenol with 2-bromothiophenol, providing a light-yellow solid; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.40-3.65 (m, 8H), 6.75 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.51 (dd, *J* = 2.1, 6.9 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.55 (t, *J* = 2.1 Hz, 1H), 7.59 (dd, *J* = 2.1, 6.9 Hz, 1H), 7.82 (dd, *J* = 2.4, 7.8 Hz, 1H), 7.92 (td, *J* = 2.4, 8.4 Hz, 1H), 8.67 (d, *J* = 2.4 Hz, 1H). MS (APCI<sup>-</sup>) (M+Cl)<sup>-</sup> at *m/z* 524, 526, 528.

Example 69(2-(Pyrrolidin-1-yl)phenyl)[2-chloro-4-( *E*-((morpholin-1-yl)carbonyl)0054795 033100  
007EE0 56274560

ethenyl phenyl] sulfide

Sub  
A28

To a stirred solution of bromide (75 mg, 0.17 mmol) from Example 12 in toluene in a sealed tube was added sequentially pyrrolidine (18.4 mL, 0.22 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3.0 mg, 0.0034 mmol), BINAP (6.0 mg, 0.010 mmol), followed by NaO*t*-Bu (26 mg, 0.27 mmol). The resulting mixture was then flushed with anhydrous N<sub>2</sub> for 2 min before it was capped and heated at 90 °C for 24 h. The reaction mixture was then allowed to cool down to room temperature and partitioned between ethyl acetate and brine. The organic layer was then dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The crude product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound (40 mg, 55% yield) as a white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.83 (br s, 4H), 3.40 (br s, 4H), 3.56-3.80 (m, 8H), 6.57 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 15.6 Hz, 1H), 6.81 (br t, *J* = 8.4 Hz, 1H), 6.90 (br s, 1H), 7.15 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.18-7.27 (m, 1H), 7.32 (td, *J* = 1.8, 8.4 Hz, 1H), 7.42 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 15.6 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 429, 431.

Example 70(2-Methoxyphenyl)-[2-chloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

The title compound was prepared according to the procedures of Example 1, giving a white solid, m.p. 162-164°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.60-3.78 (m, 8H), 3.84 (s, 3H), 6.72 (d, *J* = 9 Hz, 1H), 6.78 (d, *J* = 16 Hz, 1H), 6.96-7.04 (m, 2H), 7.16 (dd, *J* = 9 Hz, 2 Hz, 1H), 7.40-7.46 (, 2H), 7.55 (d, *J* = 2 Hz, 1H), 7.58 (d, *J* = 16 Hz, 1H).

Anal. Calcd. for  $C_{20}H_{20}ClNO_3S$ : C, 61.61; H, 5.17; N, 3.59. Found: C, 61.53, H, 5.22; N, 3.50.

Sub  
A29

### Example 71

5 (2-Isopropylphenyl)[2-nitro-4-( E-((3-carbomethoxypiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

### Example 71A

#### 1- tert-Butyloxycarbonyl -2-carbomethoxypiperazine

2-Carbomethoxypiperazine was treated with benzyl chloroformate (1.0 eq) in  
10 aqueous  $NaHCO_3$  to give 1-benzyloxycarbonyl-3-carbomethoxypiperazine. This  
material was treated with di-tert-butylidicarbonate (1.1 eq) and triethylamine (1.0 eq)  
in THF to produce 1-tert-butyloxycarbonyl-4-benzyloxycarbonyl-2-  
carbomethoxypiperazine. Hydrogenation of this compound in methanol using 10%  
Pd-C gives the title compound after filtration and solvent removal.

15 Example 71B

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carbomethoxypiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

A mixture of (2-isopropylphenyl)[2-nitro-4-E-(carboxyethenyl)phenyl]  
sulfide (prepared according to the procedures of Example 32), the amine from  
20 Example 71A (1.0 eq), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium  
tetrafluoroborate (1.0 eq), and diisopropylethylamine (2.0 eq) in DMF was stirred at  
ambient temperature for 4 hr. Ethyl acetate was added, and the mixture was washed

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sequentially with 1N HCl, bicarb, and brine. The resultant yellow solid was treated  
 with 1:1 TFA/dichloromethane at ambient temperature to give the title compound as a  
 yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.15 (d, J = 6.6 Hz, 6H); 2.52-3.16 (br  
 m, 4H); 3.25-3.47 (m, 1H); 3.60-3.65 (br d, 3H); 3.60, 3.66 (br s, br s, 3H); 6.61-6.67  
 5 (br m, 1H); 7.30-7.62 (m, 6H); 7.88-7.93 (br m, 1H); 8.58-8.65 (br m, 1H). MS  
 (APCI) (M+H)<sup>+</sup> at m/z 470. Anal calcd for C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>: C, 61.39; H, 5.80; N, 8.95.  
 Found: C, 61.51; H, 5.87; N, 8.68.

#### Example 72

10 (2-Methylphenyl)[2-nitro-4-( E-((3-carboxamido-4-carbobenzoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H  
 NMR (DMSO-d<sub>6</sub>, 300MHz) δ 2.30 (s, 3H); 2.80-4.80 (br m, 7H); 5.05-5.15 (br m,  
 2H); 6.61-6.67 (br m, 1H); 7.02-7.64 (m, 13H); 7.80-7.90 (br m, 1H); 8.56-8.65 (br m,  
 15 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 561. Anal calcd for  
 C<sub>29</sub>H<sub>28</sub>N<sub>4</sub>S<sub>1</sub>O<sub>6</sub>·0.42CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 61.66; H, 5.29; N, 9.38. Found: C, 61.41; H,  
 5.28; N, 9.53.

#### Example 73

20 (2-Isopropylphenyl)[2-nitro-4-( E-((2-carbomethoxy-4-tert-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.13 (d, J = 6.6 Hz, 6H); 1.40, 1.41 (s, s, 9H); 2.72-3.08 (br m, 1H); 3.17-3.24 (m, 1H); 3.30-3.40 (m, 1H); 3.68 (br s, 3H); 3.79-4.51 (br m, 4H); 5.06, 5.36 (br s, br s, 1H); 6.61-6.67 (m, 1H); 7.30-7.62 (m, 6H); 7.85-7.93 (br m, 1H); 8.64-8.69 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 570. Anal calcd for C<sub>29</sub>H<sub>35</sub>N<sub>3</sub>S<sub>1</sub>O<sub>7</sub>·0.15C<sub>6</sub>H<sub>14</sub>: C, 61.66; H, 6.43; N, 7.21. Found: C, 61.69; H, 6.35; N, 7.02.

#### Example 74

10 (2-Isopropylphenyl)[2-nitro-4-( E-((2-carboxy-4-tert-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 1.45 (s, 9H); 2.72-4.75 (br m, 6H); 3.38-3.49 (m, 1H); 5.78 (br s, 1H); 6.68, 6.72 (s, s, 1H); 6.88, 6.94 (br s, br, s, 1H); 7.26-7.71 (m, 6H); 8.44 (br s, 1H). MS (APCI) (M-H)<sup>+</sup> at m/z 554. Anal calcd for C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>S<sub>1</sub>O<sub>7</sub>: C, 60.53; H, 5.99; N, 7.56. Found: C, 60.42; H, 6.21; N, 7.31.

#### Example 75

20 (2-Isopropylphenyl)[2-trifluoromethyl-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.78 (s, 1H), 7.62 (d, 1H, J = 15.5 Hz), 7.43-7.49 (m,

3H), 7.37 (d, 1H,  $J = 8.1$  Hz), 7.23 (m, 1H), 6.85 (d, 1H,  $J = 15.5$  Hz), 6.82 (d, 1H,  $J = 8.5$  Hz), 3.63-3.77 (m, 6H), 3.45-3.55 (m, 3H), 2.14 (s, 3H), 1.17 (d, 6H,  $J = 6.6$  Hz). MS (ESI)  $m/z$  477, 499, 975, 953. Anal. Calcd for  $C_{25}H_{27}F_3N_2O_2S \cdot 0.5$  EtOAc: C, 62.29; H, 6.00; N, 5.38. Found: C, 62.40; H, 6.21; N, 5.35.

5

Example 76

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

10  $^1H$  NMR ( $CDCl_3$ , 300 MHz) 7.78 (s, 1H), 7.62 (br, 1H), 7.33-7.48 (m, 3H), 7.22 (m, 1H), 6.85 (m, 1H), 6.80 (d, 1H,  $J = 8.5$  Hz), 3.73 (br, 8H), 3.49 (dq, 1H,  $J_1 = J_2 = 6.9$  Hz), 1.17 (d, 6H,  $J = 7.1$  Hz). MS (ESI)  $m/z$  436, 871, 893. Anal. Calcd for  $C_{23}H_{24}F_3N_1O_2S$ : C, 63.43; H, 5.55; N, 3.22. Found: C, 63.12; H, 5.81, N, 3.10.

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Example 77

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared according to the procedures of Example 1.

20  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  7.77 (s, 1H), 7.52 (d, 1H,  $J = 15.4$  Hz), 7.43-7.51 (m, 3H), 7.36 (d, 1H,  $J = 8.8$  Hz), 7.22 (m, 1H), 7.10 (br, 1H), 6.80 (d, 1H,  $J = 8.4$  Hz), 6.44 (d, 1H,  $J = 15.4$  Hz), 3.49 (dq, 1H,  $J_1 = J_2 = 6.9$  Hz), 3.40 (m, 4H), 3.31 (dd, 2H,  $J_1 = 5.7$  Hz,  $J_2 = 12.0$  Hz), 2.44 (t, 2H,  $J = 8.1$  Hz), 2.08 (tt, 2H,  $J_1 = J_2 = 7.5$  Hz), 1.74

0054795 5627560

Sub  
A29

~~C<sub>20</sub>H<sub>29</sub> 3.42 C<sub>25</sub>: C, 65.00, H, 9.90, N, 5.71. Found: C, 64.00, H, 9.12, N, 5.00.~~

## 069473 0300

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## 15

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Anal. Calcd for  $C_{24}H_{26}F_3N_1O_1S$ : C, 66.49; H, 6.04; N, 3.23. Found: C, 66.24; H, 6.14, N, 3.06.

### Example 80

5     (2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((5-hydroxypent-1-ylamino)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.77 (s, 1H), 7.54 (d, 1H, J = 15.5 Hz), 7.43-7.49 (m, 3H), 7.33 (d, 1H, J = 8.0 Hz), 7.22 (m, 1H), 6.79 (d, 1H, J = 8.4 Hz), 6.35 (d, 1H, J = 15.6 Hz), 5.67 (br, 1H), 3.67 (t, 2H, J = 6.4 Hz), 3.49 (dq, 1H, J<sub>1</sub> = J<sub>2</sub> = 6.9 Hz), 3.40 (m, 2H), 2.40 (m, 2H), 1.45-1.62 (m, 6H), 1.17 (d, 6H, J = 7.0 Hz). MS (ESI) *m/z* 452, 474, 903, 925. Anal. Calcd for  $C_{24}H_{28}F_3NO_2S \cdot 0.56 \text{ EtOAc}$ : C, 62.92; H, 6.54; N, 2.80. Found: C, 62.86; H, 6.53; N, 2.96.

15

### Example 81

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carbomethoxy-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 2.20 (s, 3H); 2.75-3.80 (br m, 4H); 3.39-3.50 (m, 1H); 3.70, 3.77 (br s, br s, 3H); 4.49-4.75 (br m, 2H); 5.39 (br s, 1H); 6.71(m, 1H); 6.91-7.04 (br m, 1H); 7.25-7.64 (m, 6H); 8.42 (br m, 1H). MS

Found: C, 61.40; H, 6.05; N, 7.88.

5 (2-Biphenyl)[2-chloro-4-( *E*-((morpholin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

To a stirred solution of bromide from Example 12 (60 mg, 0.14 mmol) in 1 mL of toluene was added 0.5 mL of sat.  $\text{Na}_2\text{CO}_3$ ,  $\text{Pd}(\text{PPh}_3)_4$  (8 mg, 0.007 mmol), phenylboronic acid (17 mg, 0.14 mmol). The mixture was flushed with nitrogen and heated at 100 °C for 3 h. The reaction mixture was then allowed to cool down to room temperature and partitioned between ethyl acetate and brine. The organic layer was then dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The crude product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound as colorless oil (40 mg, 67% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  3.58-3.86 (m, 8H), 6.77 (d,  $J = 15.6$  Hz, 1H), 6.86 (d,  $J = 8.4$  Hz, 1H), 7.67 (dd,  $J = 2.1, 8.4$  Hz, 1H), 7.29-7.40 (m, 3H), 7.40-7.48 (m, 6H), 7.56 (d,  $J = 15.6$  Hz, 1H), 7.65 (d,  $J = 1.8$  Hz, 1H). MS (APCI $^+$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  436, 438.

20 (3,4-Dimethylphenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-  
yl)carbonyl)ethenyl)phenyl]sulfide

Sub  
A31

To a solution of the compound of Example 32A (40 mg, 0.12 mmole) in 2.5 mL of dimethylformamide was added 3,4-dimethylthiophenol (17 mg, 0.12 mmole), followed by potassium carbonate powder (20 mg, 0.14 mmole). The mixture was heated at 100°C for 20 h. The solvent was removed using N<sub>2</sub> gas flow. Water (5 mL) was then added to the residue, the resulting precipitate was collected through filtration, washed with cold water, and air dried to give the title compound (42 mg, 81%) as light yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.08 (s, 3H), 2.23 (s, 3H), 2.27 (s, 3H), 3.45 (br, m, 2H), 3.63 (br, m, 6H), 6.79 (s, 1H), 6.82 (d, J = 19 Hz, 1H), 7.18 (d, J = 19 Hz, 1H), 7.24 (dd, J = 4, 19 Hz, 1H), 7.27 (s, 1H), 7.34 (d, J = 21 Hz, 1H), 7.56 (d, J = 39 Hz, 1H), 8.32 (d, J = 4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 440. FAB High Resolution MS calculated m/z for C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 440.1644. Observed m/z: 440.1646.

#### Example 84

15      (2-Bromophenyl)[2-trifluoromethyl-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 9 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, and 3,4-dichlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, to give a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.43-3.80 (m, 8H), 7.21 (dd, J = 2.1, 8.4 Hz, 1H), 7.24 (d, J = 8.4 Hz, 1H), 7.33 (td, J = 2.1, 7.65 Hz, 1H), 7.42 (td, J = 1.8, 7.65 Hz, 1H), 7.45 (d, J = 15.6 Hz, 1H), 7.58 (d, J = 15.6 Hz, 1H), 7.78 (dd, J =

1.8, 8.4 Hz, 1H), 7.96 (dd,  $J = 1.8, 8.4$  Hz, 1H), 8.25 (d,  $J = 1.8$  Hz, 1H). MS (APCI<sup>+</sup>) ( $M+NH_4$ )<sup>+</sup> at  $m/z$  530, 532, 534.

### Example 85

5 (5-Indolyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

To a stirred solution of 5-iodoindole (255 mg, 1.05 mmol) in 5.0 mL of anhydrous DMF was added the potassium thiolate (457 mg, 1.26 mmol) from Example 65B, followed by  $K_2CO_3$  (174 mg, 1.26 mmol), and cuprous iodide (20 mg, 0.11 mmol). The resulting mixture was then heated at 120 °C for overnight. The reaction mixture was then allowed to cool to ambient temperature and poured into water. The aqueous mixture was extracted twice with 25 mL of ethyl acetate. The combined organic layer was then washed with water and brine, dried over  $Na_2SO_4$ , filtered, concentrated on a rotavap under reduced pressure. The crude product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound (115 mg, 25 % based on the iodide) as a light-brown solid.  $^1H$  NMR ( $d_6$ -DMSO, 300 MHz)  $\delta$  2.03 (s, 3H), 3.40-3.78 (m, 8H), 6.51 (d,  $J$  = 8.4 Hz, 1H), 6.53 (s, 1H), 7.23 (dd,  $J$  = 2.1, 8.4 Hz, 1H), 7.27 (d,  $J$  = 15.6 Hz, 1H), 7.39 (d,  $J$  = 15.6 Hz, 1H), 7.41 (dd,  $J$  = 1.8, 8.4 Hz, 1H), 7.49 (t,  $J$  = 2.7 Hz, 1H), 7.56 (d,  $J$  = 8.4 Hz, 1H), 7.85 (d,  $J$  = 1.8 Hz, 1H), 7.99 (d,  $J$  = 1.8 Hz, 1H). MS (APCI $^+$ ) ( $M+NH_4$ ) $^+$  at  $m/z$  440, 442. Anal. Calcd for  $C_{23}H_{22}ClN_3O_2S \cdot 0.53 CH_2Cl_2$ : C, 58.28; H, 4.79; N, 8.66. Found: C, 58.31; H, 4.93; N, 8.65.

Example 86

(5-Benzodioxolyl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)  
ethenyl) phenyl] sulfide

5 The title compound was prepared by the procedures described in Example 85 substituting 5-iodoindole with 1-iodo-3,4-methylenedioxybenzene, providing a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.14 (s, 3H), 3.48-3.60 (m, 2H), 3.60-3.84 (m, 6H), 6.05 (s, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 15.3 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 2.1 Hz, 1H), 7.08 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.19 (d, *J* = 1.8, 8.4 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 15.6 Hz, 1H). MS (APCI<sup>+</sup>) (M+NH<sub>4</sub>)<sup>+</sup> at *m/z* 445, 447.

Example 87

(2-Isopropylphenyl)[2-nitro-4-( E-((2-carbomethoxypiperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

15 Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, *J* = 6.6 Hz, 6H); 2.52-2.91 (br m, 5H); 3.30-3.40 (m, 1H); 3.68, 3.69 (s, s, 3H); 4.10-4.25 (br m, 1H); 5.00-5.21 (br m, 1H); 6.60-6.65 (m, 1H); 7.29-7.62 (m, 6H); 7.85-7.95 (m, 1H); 8.64-8.68 (m, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 470.

Example 88

Sub  
A32

148

(2,3-Dimethoxyphenyl)-[2-chloro-4-(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]  
sulfide

The title compound was prepared according to the procedures of Example 1, giving a white solid, m.p. 148-150C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.60-3.78 (m, 8H), 3.85 (s, 3H), 3.91 (s, 3H), 6.78 (d, J=16Hz, 1H), 6.86-6.98 (m, 3H), 7.20 (dd, J=9Hz, 2Hz, 1H), 7.54 (d, J=2Hz, 1H), 7.58 (d, J=16Hz, 1H). Anal. Calcd. for C<sub>21</sub>H<sub>22</sub>ClNO<sub>4</sub>S: C, 60.06; H, 5.28; N, 3.33. Found: C, 59.72; H, 5.34; N, 2.97.

Example 89

(2-Fluorophenyl)[2-nitro-4-(E-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl]phenyl]  
sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 2-fluorothiophenol. Yellow solid (40 mg, 78%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.17 (s, 3H), 3.56 (br, m, 2H), 3.77 (br, m, 6H), 6.88 (dd, J = 3, 21 Hz, 1H), 6.93 (d, J = 39 Hz, 1H), 7.26 (dd, J = 3, 21 Hz, 1H), 7.33 (dd, J = 3, 19 Hz, 1H), 7.49 (br, d, J = 20 Hz, 1H), 7.58 (m, 1H), 7.66 (m, 2H), 8.46 (d, J = 4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 430. FAB High Resolution MS calculated m/z for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>FS (M+H)<sup>+</sup>: 430.1237. Observed m/z: 430.1246.

Example 90

(2-Bromophenyl)[2-trifluoromethyl-4-(E-((4-tert-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl]phenyl]  
sulfide

Sub 31

The title compound was prepared by the procedures described in Example 1 substituting 2,4-dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, and 6-amino-1-hexanol with *t*-butyl 1-piperazinecarboxylate, to give a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.48 (s, 9H), 3.49 (br s, 4H), 3.56-3.78 (m, 4H), 6.89 (d, *J* = 15.6 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.18-7.35 (m, 3H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 15.6 Hz, 1H), 7.68 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.85 (br s, 1H). MS (APCI<sup>+</sup>) (*M*+Cl)<sup>+</sup> at *m/z* 605, 607, 609. Anal. Calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>BrF<sub>3</sub>S · 0.03 H<sub>2</sub>O: C, 52.50; H, 4.59; N, 4.90. Found: C, 52.54; H, 4.71; N, 4.68.

10

Example 91

(2-(Pyrrolidin-1-yl)phenyl)[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 69 substituting the bromide from Example 12 with the bromide from Example 90, to give a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.85 (s, 9H), 1.85 (br s, 4H), 3.32-3.55 (m, 8H), 3.55-3.78 (m, 4H), 6.76 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 15.6 Hz, 1H), 7.23-7.45 (m, 5H), 7.61 (d, *J* = 15.6 Hz, 1H), 7.75 (br s, 1H). MS (APCI<sup>+</sup>) (*M*+H)<sup>+</sup> at *m/z* 562.

20

Example 92

(3-Carboxamidophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)

ethenyl) phenyl] sulfide

Example 92A

(3-Carboxyphenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)

5

ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 32B substituting 2,4-dichlorothiophenol with 3-mercaptopbenzoic acid.

Example 92B

10

(3-Carboxamidophenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)

ethenyl) phenyl] sulfide

To a stirred solution of benzoic acid from Example 92A (40 mg, 0.088 mmol) in 1 mL of anhydrous DMF with HOBT (15 mg, 0.097 mmol) was added EDAC (19 mg, 0.097 mmol), followed by ammonium chloride (large excess). The pH of the solution was adjusted to 6 with addition of triethylamine. The resulting mixture was then stirred at ambient temperature for 6 h. Water was added to quench the reaction. The product precipitated out after stirring for 30 min, which was then isolated by filtration and dried in vacuum oven to give a light yellow solid (25 mg, 63% yield). <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.43-3.82 (m, 8H), 6.84 (d, *J* = 8.7 Hz, 1H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 15.6 Hz, 1H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.66 (t, *J* = 7.65 Hz, 1H), 8.06 (d, *J* = 7.80 Hz, 1H), 8.12 (s, 2H), 8.67 (d, *J* = 2.1 Hz, 1H). MS (ESI<sup>+</sup>) (M+Na)<sup>+</sup> at *m/z* 477.

00541795 033100

SUB  
A32

15

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Example 93

(3-(Hydroxymethyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Sub  
A<sub>33</sub><sup>5</sup>

To a stirred solution of benzoic acid from Example 92A (255 mg, 0.56 mmol) in 5 mL of anhydrous THF at 0 °C was added in turn Et<sub>3</sub>N (102 mL, 0.73 mmol) and ethyl chloroformate (70 mL, 0.73 mmol). After 60 min, the reaction mixture was filtered through celite plug into a stirred solution of NaBH<sub>4</sub> in water at 0 °C. The resulting reaction mixture stirred at 0 °C for 2 h before it was extracted with EtOAc (2×20 mL). The combined organic layers was washed with 3N HCl, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure. The crude product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound (80 mg, 32% yield) as a light-yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.40-3.79 (m, 8H), 4.56 (s, 2H), 5.38 (br s, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.52 (br s, 3H), 7.57 (br s, 2H), 7.91 (dd, *J* = 2.1, 8.7 Hz, 1H), 8.66 (d, *J* = 2.1 Hz, 1H). MS (APCI<sup>+</sup>) (M+NH<sub>4</sub>)<sup>+</sup> at *m/z* 459.

Example 94

Phenyl[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was obtained as a reductive side product from the reaction mixture described in Example 91, as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ

1.49 (s, 9H), 3.43-3.56 (br s, 4H), 3.56-3.82 (m, 4H), 6.85 (d,  $J = 15.6$  Hz, 1H), 7.06 (d,  $J = 8.4$  Hz, 1H), 7.37-7.50 (m, 4H), 7.63 (d,  $J = 15.6$  Hz, 1H), 7.67 (d,  $J = 8.4$  Hz, 1H), 7.76 (d,  $J = 11.7$  Hz, 1H), 7.80 (s, 1H). MS (APCI) ( $M+Cl$ )<sup>-</sup> at  $m/z$  527.

5

Example 95

(2-Isopropylphenyl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxy-4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 71.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  7.79 (s, 1H), 7.62 (d, 1H,  $J = 15.0$  Hz), 7.48 (d, 1H,  $J = 7.2$  Hz), 7.43 (m, 2H), 7.38 (d, 1H,  $J = 8.1$  Hz), 7.22 (m, 1H), 6.86 (d, 1H,  $J = 15.4$  Hz), 6.80 (d, 1H,  $J = 8.4$  Hz), 5.30 (br, 1H), 4.62 (br d, 2H,  $J = 14.0$  Hz), 3.89 (br m, 1H), 3.76 (s, 3H), 3.49 (dq, 1H,  $J_1 = J_2 = 6.9$  Hz), 3.12 (m, 2H), 2.94 (br, 1H), 1.46 (s, 9H), 1.17 (d, 6H,  $J = 6.6$  Hz). MS (ESI)  $m/z$  -591, -627, -677.

15

Example 96

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-(pyridine-4-methylaminocarbonyl)-4-*tert*-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300MHz)  $\delta$  1.14 (d,  $J = 6.6$  Hz, 6H); 1.38 (s, 9H); 2.83-3.85 (br m, 5H); 4.09-4.51 (br m, 4H); 4.91-5.09 (br m, 1H); 6.64 (d,  $J = 8.5$  Hz, 1H); 7.12-7.62 (m, 8H); 7.82-7.96 (m, 1H); 8.26-8.48 (m, 2H); 8.63-8.75 (m, 2H). MS (APCI)

(M+H)<sup>+</sup> at m/z 646. Anal calcd for C<sub>34</sub>H<sub>39</sub>N<sub>3</sub>S<sub>1</sub>O<sub>6</sub>: C, 63.24; H, 6.09; N, 10.84. Found: C, 63.07; H, 6.43; N, 10.54.

Example 97

5 (2-Ethoxyphenyl)-[2-chloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

Example 97A2-Ethoxybenzenethiol

To 7.82g of ethoxybenzene and 7.41g of tetramethylethylenediamine in 75 ml ether, cooled in an ice bath, a solution of 25.6 ml of a 2.5 M n-butyllithium solution in  
10 hexane, was added dropwise under a nitrogen atmosphere. The mixture was stirred for 1 hour at room temperature and then cooled to -65 degrees. Sulfur (2.28 g) was added in portions. The mixture was stirred for 3 hours at room temperature and then cooled in ice. LiAlH<sub>4</sub> (0.6 g) was added and the mixture was stirred 1 hour at room temperature. The mixture was again cooled in ice while 5 ml water was added  
15 dropwise followed by 15% HCl in water until all salts. The aqueous phase was separated and washed with ether. The combined ether layers was washed with HCl, then water. After drying with Na<sub>2</sub>SO<sub>4</sub>, the ether was evaporated to give 9.66 g of product. NMR analysis showed 70% pure material with 30% of a diaryl sulfide impurity. This mixture was carried forward to the next step.

20

Example 97B

(2-Ethoxyphenyl)-[2-chloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

Sub  
A34  
00541795, 033100  
DOYEE "SSCTH560"

The title compound was prepared according to the procedures of Example 1, substituting the thiol of Example 97A, giving a white solid, m.p. 125-127C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.25 (t, J=7Hz, 3H), 3.60-3.78 (m, 8H), 4.05 (q, J=7Hz, 2H), 6.76 (d, J=15Hz, 1H), 6.82 (d, J=9H, 1H), 6.94-7.00 (m, 2H), 7.16 (dd, J=9Hz, 2H, 5 1H), 7.34-7.45 (m, 2H), 7.54 (d, J=2Hz, 1H), 7.58 (d, J=15Hz, 1H). Anal. Calcd. for C<sub>21</sub>H<sub>22</sub>ClNO<sub>3</sub>S: C, 62.44; H, 5.49; N, 3.47. Found: C, 62.14; H, 5.70; N, 3.22.

#### Example 98

10 (2-Methoxyphenyl)[2-nitro-4-( E-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 2-methoxythiophenol, giving a yellow solid (40 mg, 77%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.14 (s, 3H), δ 3.54 (br, m, 2H), δ 3.68 (br, m, 6H), δ 3.79 (s, 3H), δ 6.81 (d, J = 21 Hz, 1H), δ 6.89 (d, J = 39 Hz, 1H), δ 7.03 15 (d, J = 21 Hz, 1H), δ 7.08 (m, 1H), δ 7.41 (br, d, J = 21 Hz, 1H), δ 7.53 (m, 1H), δ 7.60 (m, 1H), δ 7.65 (br, s, 1H), δ 8.42 (br, s, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 442.

#### Example 99

20 (2-(Azetidin-1-yl)phenyl)[2-trifluoromethyl-4-( E-((4-(tert-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 69 substituting pyrrolidine with azetidine hydrochloride, and the bromide from Example

12 with bromide from Example 90, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.48 (s, 9H), 2.18 (pentet, *J* = 7.43 Hz, 2H), 3.40-3.53 (m, 4H), 3.53-3.77 (m, 4H), 4.02 (t, *J* = 7.43 Hz, 4H), 6.54 (d, *J* = 8.7 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.78 (tt, *J* = 1.5, 7.35 Hz, 1H), 6.81 (d, *J* = 15.6 Hz, 1H), 7.29-7.42 (m, 3H), 7.61 (d, *J* = 15.6 Hz, 1H), 7.75 (br s, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 548.

#### Example 100

(2-(Piperidin-1-yl)phenyl)[2-trifluoromethyl-4-(*E*-((4-(*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

10 The title compound was prepared by the procedures described in Example 69 substituting pyrrolidine with piperidine, and the bromide from Example 12 with bromide from Example 90, and isolated as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.48 (s, 9H), 1.54 (br s, 6H), 2.96 (br s, 4H), 3.48 (br s, 4H), 3.55-3.78 (m, 4H), 6.86 (d, *J* = 15.6 Hz, 1H), 6.99 (td, *J* = 1.8, 7.5 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.25 (br m, 1H), 7.31 (td, *J* = 1.8, 7.5 Hz, 1H), 7.42 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.65 (d, *J* = 15.6 Hz, 1H), 7.71 (d, *J* = 1.8 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 576.

#### Example 101

20 (3-Chloro-2-formylphenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 65B substituting 2,3-dichlorobenzaldehyde with 2,6-dichlorobenzaldehyde, isolated as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.05 (s, 3H), 3.56 (br s, 2H), 3.61-3.86 (m, 6H), 6.68 (q, *J* = 3.0 Hz, 1H), 6.93 (d, *J* = 15.6 Hz, 1H), 7.23 (d, *J* = 3.0 Hz, 1H), 7.25 (m, 1H), 7.45 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 15.6 Hz, 1H), 7.69 (d, *J* = 2.1 Hz, 1H). MS (APCI<sup>+</sup>) (*M*+H)<sup>+</sup> at *m/z* 463, 465, 467.

#### Example 102

(2-Trifluoromethylphenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.84 (s, 1H), 7.80 (m, 1H), 7.66 (d, 1H, *J* = 15.4 Hz), 7.49 (m, 3H), 7.40 (m, 1H), 7.06 (d, 1H, *J* = 8.0 Hz), 6.87 (d, 1H, *J* = 15.4 Hz), 3.62-3.80 (m, 6H), 3.53 (m, 2H), 2.15 (s, 3H). MS (ESI) *m/z* 503, 525, 1027.

#### Example 103

(3-Bromophenyl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.83 (s, 1H), 7.66 (d, 1H, *J* = 15.4 Hz), 7.57 (t, 1H, *J* = 1.9 Hz), 7.49 (m, 2H), 7.36 (dt, 1H, *J* = 1.6, 7.8 Hz), 7.24 (m, 1H), 7.18 (d, 1H, *J* =

8.1 Hz), 6.87 (d, 1H, J = 15.2 Hz), 3.62-3.82 (m, 6H), 3.54 (m, 2H), 2.15 (s, 3H). MS (ESI)  $m/z$  514, 515, 535, 537.

#### Example 104

5     (3,5-Dimethylphenyl)[2-trifluoromethyl-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.79 (s, 1H), 7.64 (d, 1H, J = 15.1 Hz), 7.42 (d, 1H, J = 8.8 Hz), 7.49 (m, 2H), 7.13 (s, 2H), 7.04 (s, 2H), 6.84 (d, 1H, J = 15.2 Hz), 3.62-3.82 (m, 6H), 3.54 (m, 2H), 2.32 (s, 6H), 2.15 (s, 3H). MS (ESI)  $m/z$  463, 485, 925, 947.

#### Example 105

15     (2-Isopropylphenyl)[2-nitro-4-( E-((3-dimethylaminocarbonyl)-4-(pyridine-4-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 2.50-3.83 (br m, 10H); 4.04-4.66 (br m, 3H); 5.32-5.43 (br m, 1H); 6.60-6.69 (m, 1H); 7.15-7.64 (m, 8H); 7.85-7.93 (m, 1H); 8.59-8.72 (m, 3H). MS (APCI) (M+H)<sup>+</sup> at  $m/z$  588. Anal calcd for C<sub>31</sub>H<sub>33</sub>N<sub>5</sub>S<sub>1</sub>O<sub>5</sub>·0.67H<sub>2</sub>O: C, 62.07; H, 5.77; N, 11.68. Found: C, 62.13; H, 6.01; N, 11.48.

Example 106

(2-Isopropylphenyl)[2-nitro-4-( E-((3-dimethylaminocarbonyl-4-carbomethoxypiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

5 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 2.50-3.83 (br m, 14H); 4.16-4.63 (br m, 2H); 4.98 (br s, 1H); 6.60-6.69 (m, 1H); 7.20-7.61 (m, 6H); 7.85-7.93 (m, 1H); 8.59-8.65 (m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 541.

Example 107

10 (2-Isopropylphenyl)[2-nitro-4-( E-((3-dimethylaminocarbonyl-4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 1.88, 2.04 (s, s, 3H); 2.50-3.83 (br m, 11H); 4.16-4.59 (br m, 2H); 5.04-5.25 (br m, 1H); 6.60-6.69 (m, 1H); 15 7.21-7.62 (m, 6H); 7.85-7.93 (m, 1H); 8.58-8.65 (m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 525. Anal calcd for C<sub>27</sub>H<sub>32</sub>N<sub>4</sub>S<sub>1</sub>O<sub>5</sub>: C, 61.81; H, 6.15; N, 10.68. Found: C, 61.93; H, 6.75; N, 9.67.

Example 108

20 (2-Isopropylphenyl)[2-nitro-4-( E-((3-(1-morpholinocarbonyl)-4-tert-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

00446" 56/7/560

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.11-1.16 (br m, 6H); 1.35, 1.40 (br s, br s, 9H); 2.67-5.0 (br m, 16H); 6.60-6.69 (m, 1H); 7.28-7.62 (m, 6H); 7.87-7.92 (m, 1H); 8.63-8.67 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 625. Anal calcd for C<sub>32</sub>H<sub>40</sub>N<sub>4</sub>S<sub>1</sub>O<sub>7</sub>: C, 61.52; H, 6.45; N, 8.97. Found: C, 61.10; H, 6.65; N, 8.60.

#### Example 109

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(pyridine-4-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 2.50-4.46 (br m, 10H); 6.63 (d, J = 8.5 Hz, 1H); 7.20-7.64 (m, 8H); 7.85-7.93 (m, 1H); 8.43-8.65 (m, 4H). MS (APCI) (M+H)<sup>+</sup> at m/z 546. Anal calcd for C<sub>29</sub>H<sub>31</sub>N<sub>5</sub>S<sub>1</sub>O<sub>4</sub>·0.46CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 63.20; H, 5.96; N, 11.95. Found: C, 63.29; H, 6.27; N, 11.97.

#### Example 110

(2-Isopropylphenyl)[2-nitro-4-( E-(((3-dimethylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 2.50-3.20 (br m, 4H); 2.82 (s, 3H); 3.04 (s, 3H); 3.26-3.49 (m, 1H); 3.52-3.59 (m, 1H); 4.08-4.47 (br m, 2H); 6.63 (d, J = 8.5 Hz, 1H); 7.31-7.62 (m, 6H); 7.86-7.92 (m, 1H); 8.61 (br m, 1H). MS

(APCI) (M+H)<sup>+</sup> at m/z 483. Anal calcd for C<sub>25</sub>H<sub>30</sub>N<sub>4</sub>S<sub>1</sub>O<sub>4</sub>·0.39CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 61.71; H, 6.46; N, 10.84. Found: C, 61.96; H, 6.69; N, 10.73.

### Example 111

5        (2-Isopropylphenyl)[2-nitro-4-( E-((3-(benzylaminocarbonyl)-4-tert-  
         butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 1.33, 1.42 (br s, br s, 9H);  
2.75-4.77 (br m, 10H); 6.60-6.66 (br m, 1H); 7.02-7.94 (br m, 12H); 8.47-8.67 (m,  
10    2H). MS (APCI) (M+H)<sup>+</sup> at m/z 645.

### Example 112

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(dimethylaminocarbonyl)-4-tert-  
         butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

15        Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 1.35, 1.40 (br s, br s, 9H)  
2.50-4.99 (br m, 14H); 6.60-6.69 (m, 1H); 7.21-7.62 (m, 6H); 7.86-7.92 (m, 1H);  
8.59-8.63 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 583. Anal calcd for  
C<sub>30</sub>H<sub>38</sub>N<sub>4</sub>S<sub>1</sub>O<sub>6</sub>·0.21C<sub>6</sub>H<sub>14</sub>: C, 62.50; H, 6.87; N, 9.32. Found: C, 62.28; H, 7.15; N,

20    9.11.

Example 113

Sub  
A 35

(2-Bromophenyl)[2-chloro-4-(E-((3-(5S-hydroxymethyl)pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl]phenyl]sulfide

Sub A35  
0044795-033100

(2-Bromophenyl)[2-chloro-4-(2-carboxy-E-ethenyl) phenyl]sulfide was prepared by the procedures described in Example 1 substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde. 1-(3-aminopropyl)-5-((S)-thexyldimethylsilyloxymethyl)-2-pyrrolidinone (0.2818g, 0.8959 mmol) was added to a solution of this cinnamic acid (0.3312g, 0.8959 mmol), 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (0.3435g, 1.79 mmol), and 1-hydroxybenzotriazole hydrate (0.1816g, 1.34 mmol) in DMF (4.0 mL). After stirring for 12h the reaction mixture was diluted with EtOAc (250 mL), extracted with sat.  $\text{NH}_4\text{Cl}$  (1x75 mL), extracted with  $\text{H}_2\text{O}$  (2x75 mL), rinsed with brine (75mL), and dried over  $\text{Na}_2\text{SO}_4$ . The resultant thexyldimethylsilyl alcohol was purified by flash chromatography (EtOAc) on silica gel (.4974 g, 83%). Tetrabutylammonium fluoride (.68 mL of 1.0 M solution in THF) was added dropwise to a solution of this protected alcohol (0.4544 g, 0.682 mmol) in THF (1.7 mL). After 2h the reaction was diluted with EtOAc (50 mL) and extracted with sat.  $\text{NH}_4\text{Cl}$  (1x25 mL), extracted with  $\text{H}_2\text{O}$  (2x25 mL), rinsed with brine (25mL), and dried over  $\text{Na}_2\text{SO}_4$ . Flash chromatography (EtOAc  $\rightarrow$  9:1  $\text{CH}_2\text{Cl}_2$ :MeOH) on silica gel yielded the title compound (.3144g, 88%).  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ , 300MHz)  $\delta$  8.14 (t,  $J = 5.5$  Hz, 1H), 7.81 (m, 2H), 7.53 (dd,  $J = 8.3, 1.7$  Hz, 1H), 7.44 (dt,  $J = 7.7, 1.5$ , 1H), 7.40 (dt,  $J = 7.7, 1.8$ , 1H), 7.39 (d,  $J = 15.6$  Hz, 1H), 7.28 (dd,  $J = 7.7, 1.8$

Hz, 1H), 7.05 (d,  $J = 8.1$  Hz, 1H), 6.67 (d,  $J = 15.6$  Hz, 1H), 4.84 (t,  $J = 5.1$  Hz, 1H), 2.94-3.62 (m, 8H), 1.54-2.29 (m, 6H), MS(APCI) (M+H)<sup>+</sup> at  $m/z$  523, 525, 527, 529.

Sub  
A35

#### Example 114

5 (2-Bromophenyl)[2-chloro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)  
ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 1 substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde, and 6-amino-1-hexanol with 1-(3-aminopropyl)- 2-pyrrolidinone. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz)  $\delta$  8.12 (t,  $J = 5.9$  Hz, 1H), 7.81 (m, 2H), 7.52 (dd,  $J = 8.1, 2.0$  Hz, 1H), 7.44 (dt,  $J = 7.5, 1.4$ , 1H), 7.34 (dt,  $J = 7.5, 2.0$ , 1H), 7.39 (d,  $J = 15.8$  Hz, 1H), 7.28 (dd,  $J = 7.6, 1.9$  Hz, 1H), 7.05 (d,  $J = 8.1$  Hz, 1H), 6.67 (d,  $J = 15.8$  Hz, 1H), 4.02 (d,  $J = 7$  Hz, 1H), 3.29-3.35 (m, 2H), 3.11-3.25 (m, 4H), 2.21 (t,  $J = 8.1$  Hz, 1H), 1.94 (m, 2H), 1.64 (m, 2H), MS(APCI) (M+H)<sup>+</sup> at  $m/z$  493, 495, 497, 499.

#### Example 115

(2-Bromophenyl)[2-chloro-4-(E-(N-methyl-N-(3-(pyrrolidin-2-on-1-yl)prop-1-yl)amino)carbonyl) ethenyl)phenyl]sulfide

20 The title compound was prepared by the procedures described in Example 1 substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde, and 6-amino-1-hexanol with 1-(3-

DATE: 03-11-2005

methylaminopropyl)-2-pyrrolidinone. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.06 (d, *J* = 1.5 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.64 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.25-7.46 (m, 5H), 7.04 (d, *J* = 8.1, 1.1, 1H), 3.14-5.30 (m, 6H), 3.14 (s, 1H), 2.91 (s, 2H), 2.19 (m, 2H), 1.92 (m, 2H), 1.68 (m, 2H), MS(APCI) (M+H)<sup>+</sup> at *m/z* 507, 509, 511, 513.

5

Example 116

(2-[2-Methoxy]ethoxyphenyl)-[2-chloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

The title compound was prepared according to the procedures of Example 97, substituting 2-methoxyethoxybenzene, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.29 (s, 3H), 3.60 (t, *J*=7Hz, 2H), 3.60-3.78 (m, 8H), 4.12 (t, *J*=7Hz, 2H), 6.78 (d, *J*=15Hz, 1H), 6.82 (d, *J*=9Hz, 1H), 6.95-7.03 (m, 2H), 7.18 (dd, *J*=9Hz, 2H, 1H), 7.36-7.45 (m, 2H), 7.52 (d, *J*=2Hz, 1H), 7.57 (d, *J*=15Hz, 1H). Anal. Calcd. for C<sub>22</sub>H<sub>24</sub>ClNO<sub>4</sub>S: C, 60.85; H, 5.57; N, 3.22. Found: C, 60.65; H, 5.59; N, 3.12.

15

Example 117

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(morpholinocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, *J* = 6.6 Hz, 6H); 2.50-3.40 (br m, 6H); 3.42-3.64 (br m, 8H); 4.07-4.44 (br m, 2H); 4.08-4.47 (br m, 2H); 6.64 (d, *J* = 8.5 Hz, 1H); 7.31-7.62 (m, 6H); 7.87-7.92 (m, 1H); 8.61 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z*

0054795.03100

525. Anal calcd for  $C_{27}H_{32}N_4S_1O_5 \cdot 1.57H_2O$ : C, 58.64; H, 6.41; N, 10.13. Found: C, 58.69; H, 6.36; N, 9.78.

### Example 118

5      (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 1.41 (s, 9H); 3.30-3.40 (m, 1H); 3.50-3.72 (br m, 8H); 6.64 (d, J = 8.5 Hz, 1H); 7.34-7.62 (m, 6H); 7.87-7.92 (dd, 10 J = 8.5, 1.5 Hz, 1H); 8.65 (d, J = 1.5 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 512. Anal calcd for  $C_{27}H_{33}N_3S_1O_5$ : C, 63.38; H, 6.50; N, 8.21. Found: C, 63.69; H, 6.62; N, 7.87.

### Example 119

15      (2-Isopropylphenyl)[2-nitro-4-(*E*-((4-methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 3.62 (s, 3H); 3.30-3.38 (m, 1H); 3.38-3.72 (br m, 8H); 6.64 (d, J = 8.8 Hz, 1H); 7.34-7.62 (m, 6H); 7.87-7.92 (dd, J = 8.8, 2.0 Hz, 1H); 8.64 (d, J = 2.0 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 470. Anal 20 calcd for  $C_{24}H_{27}N_3S_1O_5 \cdot 0.34C_6H_{14}$ : C, 62.77; H, 6.27; N, 8.44. Found: C, 62.70; H, 6.33; N, 8.27.

Example 120

(2-Isopropylphenyl)[2-nitro-4-( E-(4-(pyridine-4-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

5 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 3.30-3.40 (m, 1H); 3.52-3.86 (br m, 8H); 6.61-6.66 (br m, 1H); 7.30-7.62 (m, 8H); 7.83-7.96 (br m, 1H); 8.60-8.71 (m, 3H). MS (APCI) (M+H)<sup>+</sup> at m/z 517. Anal calcd for C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>S<sub>1</sub>O<sub>4</sub>·0.38CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 64.46; H, 5.69; N, 10.19. Found: C, 64.52; H, 5.94; N, 10.21.

10

Example 121

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(pyridine-3-methylaminocarbonyl)-4-tert-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Yellow solid; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.31-1.46 (br m, 9H); 3.30-3.41 (m, 1H); 3.15-4.78 (br m, 9H); 6.61-6.67 (br m, 1H); 7.05-7.95 (br m, 9H); 8.20-8.65 (br m, 4H). MS (APCI) (M+H)<sup>+</sup> at m/z 646. Anal calcd for C<sub>34</sub>H<sub>39</sub>N<sub>5</sub>S<sub>1</sub>O<sub>6</sub>·0.13H<sub>2</sub>O: C, 62.97; H, 6.49; N, 10.79. Found: C, 62.66; H, 6.26; N, 10.60.

20

Example 122

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(pyridine-2-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0Hz, 6H); 3.30-3.41 (m, 1H); 2.50-4.46 (br m, 9H); 6.64 (d, J = 8.5 Hz, 1H); 7.21-7.93 (br m, 10H); 8.45-8.65 (br m, 3H). MS (APCI) (M+H)<sup>+</sup> at m/z 546.

5

#### Example 123

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(pyridine-3-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H

10 NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 2.50-4.41 (br m, 10H); 6.61-6.67 (br m, 1H); 7.26-7.70 (br m, 8H); 7.86-7.94 (br m, 1H); 8.40-8.67 (br m, 4H). MS (APCI) (M+H)<sup>+</sup> at m/z 546.

#### Example 124

15 (4-Hydroxyphenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 4-hydroxythiophenol. Yellow solid (23 mg, 45%); <sup>1</sup>H-NMR (Pyridine-d<sub>5</sub>, 500 MHz) δ 2.08 (s, 3H), 3.42 (br, m, 2H), 3.76 (br, m, 6H), 7.01 (d, J = 17 Hz, 1H), 7.26 (m, 2H), 7.37 (d, J = 31 Hz, 1H), 7.59 (m, 3H), 8.02  
20 (d, J = 31 Hz, 1H), 8.60 (d, J = 4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 428. FAB

High Resolution MS calculated  $m/z$  for  $C_{21}H_{22}N_3O_5S$  ( $M+H$ )<sup>+</sup>: 428.1280. Observed  $m/z$ : 428.1296.

### Example 125

5                    (3,5-Dichlorophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

NOTE: "SAFE" 007560

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 3,5-dichlorothiophenol. Yellow solid (12 mg, 21%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.04 (s, 3H), 3.43 (br, m, 2H), 3.62 (br, m, 10 6H), 6.82 (d, *J* = 22 Hz, 1H), 6.82 (d, *J* = 38 Hz, 1H), 7.37 (s, 1H), 7.38 (s, 1H), 7.40 (m, 1H), 7.43 (dd, *J* = 3, 21 Hz, 1H), 7.55 (d, *J* = 38 Hz, 1H), 8.29 (d, *J* = 4 Hz, 1H). MS (APCI) ( $M+H$ )<sup>+</sup> at  $m/z$  480. FAB High Resolution MS calculated  $m/z$  for  $C_{21}H_{20}N_3O_4Cl_2S$  ( $M+H$ )<sup>+</sup>: 480.0552. Observed  $m/z$ : 480.0553.

15

### Example 126

(2-Bromophenyl)[2-chloro-4-(*E*-((3-(5*S*-acetoxymethyl-pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

Sub A36

To a solution of the compound of Example 113 (0.0466g, 0.0889 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (.5 mL) was added triethylamine (0.024 mL, 0.18 mmol) and acetic anhydride 20 (0.0088 mL, 0.0933 mmol). After 12 h the reaction was diluted with MeOH (1.5 mL) and purified by preparative HPLC to provide the title compound (.0458 g, 91%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.14 (t, *J* = 5.7 Hz, 1H), 7.80 (m, 2H), 7.53 (dd, *J* = 8.5,

1.5 Hz, 1H), 7.45 (dt,  $J = 7.7, 1.5$ , 1H), 7.35 (dt,  $J = 7.7, 1.8$ , 1H), 7.39 (d,  $J = 15.6$  Hz, 1H), 7.29 (dd,  $J = 7.7, 1.8$  Hz, 1H), 7.05 (d,  $J = 8.1$  Hz, 1H), 6.67 (d,  $J = 15.6$  Hz, 1H), 4.20 (dd,  $J = 11.8, 3.7$  Hz, 1H), 4.03 (dd,  $J = 11.8, 4.0$  Hz, 1H), 3.85 (m, 1H), 3.45 (m, 2H), 3.15 (m, 2H), 2.95 (m, 2H), 2.00-2.48 (m, 2H), 2.02 (s, 3H), 1.51-1.82 (m, 2H), MS(APCI) (M+H)<sup>+</sup> at  $m/z$  565, 567, 569, 571.

### Example 127

(2-Bromophenyl)[2-chloro-4-(E-((3-(5S-methoxymethyl-pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

10 Sodium hydride (0.0088g, 0.22 mmol, 60% dispersion) was added to a solution of the compound of Example 113 (0.0524g, 0.1 mmol) in DMF (0.5 mL). After 15 min, iodomethane (0.025 mL, 0.4 mmol) was added and the reaction was stirred for 12 h. The reaction was diluted with EtOAc (7 mL) and extracted with sat. NH<sub>4</sub>Cl (1x2.5 mL), extracted with H<sub>2</sub>O (2x2.5 mL), rinsed with brine (2.5mL), dried

15 over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated *in vacuo*. The crude products were diluted with MeOH (1.5 mL) and purified by preparative HPLC to provide the title compound (0.0408 g, 74%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz)  $\delta$  8.07 (2, 1H), 7.80 (dd,  $J = 7.9, 1.3$  Hz, 1H), 7.64 (dd,  $J = 8.3, 1.6$  Hz, 1H), 7.23-7.46 (m, 5H), 7.04 (d,  $J = 8.1, 1H$ ), 3.74 (m, 1H), 4.4-3.52 (m, 6H), 3.27 (s, 1.5H), 3.22 (s, 1.5H), 3.14 (s, 1.5H), 2.91 (s,

20 1.5H), 1.5-2.3 (m, 6H), MS(APCI) (M+H)<sup>+</sup> at  $m/z$  551, 553, 555.

### Example 128

Sub  
A34

(2-Bromophenyl)[2-chloro-4-(E-((3-(4*R*-hydroxymethyl-pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described for Example 113 substituting 1-(3-aminopropyl)-5-((*S*)-thexyldimethylsilyloxymethyl)-2-pyrrolidinone with 1-(3-aminopropyl)-4-((*R*)-thexyldimethylsilyloxy)-2-pyrrolidinone. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.13 (t, *J* = 5.5 Hz, 1H), 7.80 (m, 2H), 7.53 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.27-7.44 (m, 4H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 15.8 Hz, 1H), 5.19 (d, *J* = 3.7 Hz, 1H), 4.28 (br s, 1H), 3.10-3.62 (m, 8H), 2.06 (dd, 1H), 1.63 (m, 1H), MS(APCI) (M+H)<sup>+</sup> at *m/z* 509, 511, 513.

#### Example 129

Phenyl[2-nitro-4-(E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with thiophenol. Yellow solid (36 mg, 73%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.20 (s, 3H), 3.59 (br, m, 2H), 3.78 (br, m, 6H), 6.92 (d, *J* = 21 Hz, 1H), 6.95 (d, *J* = 39 Hz, 1H), 7.49 (br, d, *J* = 21 Hz, 1H), 7.56 (m, 3H), 7.65 (m, 2H), 7.69 (d, *J* = 38 Hz, 1H), 8.46 (d, *J* = 4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at *m/z* 412. FAB High Resolution MS calculated *m/z* for C<sub>21</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 412.1331. Observed *m/z*: 412.1342.

#### Example 130

(2-Dimethylaminophenyl)[2-nitro-4-(E-((4-acetylpiperazin-1-yl)carbonyl)

ethenyl) phenyl] sulfide

To a stirred solution of aniline from Example 47 (21 mg, 0.049 mmol) in 1 mL of ethanol was added Me<sub>2</sub>SO<sub>4</sub> (14.0 mL, 0.15 mmol) followed by sat. Na<sub>2</sub>CO<sub>3</sub> (25 mL). The mixture was then refluxed for one day. The reaction mixture was allowed to cool down to ambient temperature, partitioned between EtOAc and water. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated under reduced pressure. The residue was then purified on a Gilson Preparative HPLC as described in Example 38B to give the title compound (10 mg, 45% yield), as a light yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.16 (s, 3H), 2.83 (s, 3H), 3.32 (br s, 3H), 3.47-3.85 (m, 8H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 15.6 Hz, 1H), 7.40-7.51 (m, 3H), 7.64 (d, *J* = 15.6 Hz, 1H), 8.45 (d, *J* = 1.8 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 454.

Example 131

(3-((2-Hydroxyethyl)aminocarbonyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 92B, substituting ammonium chloride with ethanolamine, to give a light yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.30-3.79 (m, 12H), 4.75 (t, *J* = 5.7 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.92 (dd, *J* = 2.1, 8.1 Hz, 1H), 8.04

(d,  $J = 8.4$  Hz, 1H), 8.11 (s, 1H), 8.62 (t,  $J = 5.7$  Hz, 1H), 8.66 (d,  $J = 2.1$  Hz, 1H). MS (APCI) ( $M+Cl$ )<sup>-</sup> at  $m/z$  533, 535.

### Example 132

5    (3-((3-(1-Imidazolyl)propyl)aminocarbonyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

      The title compound was prepared by the procedures described in Example 92B, substituting ammonium chloride with 3-aminopropyl-1-imidazole, as a light yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.96 (quintet,  $J = 6.98$  Hz, 2H), 2.04  
10    (s, 3H), 3.24 (q,  $J = 6.98$  Hz, 2H), 3.35-3.95 (m, 8H), 4.02 (t,  $J = 6.98$  Hz, 2H), 6.87 (d,  $J = 8.4$  Hz, 1H), 6.88 (s, 1H), 7.19 (s, 1H), 7.41 (d,  $J = 15.6$  Hz, 1H), 7.54 (d,  $J = 15.6$  Hz, 1H), 7.64 (s, 1H), 7.68 (d,  $J = 7.8$  Hz, 1H), 7.79 (dt,  $J = 1.8, 7.8$  Hz, 1H), 7.91 (dd,  $J = 1.8, 8.7$  Hz, 1H), 8.03 (d,  $J = 7.8$  Hz, 1H), 8.09 (t,  $J = 1.8$  Hz, 1H), 8.65 (d,  $J = 1.8$  Hz, 1H). MS (APCI) ( $M+Cl$ )<sup>-</sup> at  $m/z$  597, 599.

15

### Example 133

(3-((2-(1-Morpholinyl)ethyl)aminocarbonyl)phenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

      The title compound was prepared by the procedures described in Example  
20    92B, substituting ammonium chloride with 2-aminoethyl-1-morpholine, as a light yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 2.44 (br s, 4H), 3.20-3.80 (m, 16H), 6.87 (d,  $J = 8.4$  Hz, 1H), 7.41 (d,  $J = 15.6$  Hz, 1H), 7.54 (d,  $J = 15.6$  Hz,

1H), 7.68 (d,  $J = 8.4$  Hz, 1H), 7.79 (d,  $J = 8.4$  Hz, 1H), 7.91 (dd,  $J = 2.1, 8.4$  Hz, 1H), 8.02 (d,  $J = 8.4$  Hz, 1H), 8.07 (s, 1H), 8.58 (t,  $J = 6.0$  Hz, 1H), 8.65 (d,  $J = 2.1$  Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  568.

5

Example 134

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-hydroxymethyl-4-*tert*-butoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl] phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300MHz)  $\delta$  1.14 (d,  $J = 7.0$  Hz, 6H); 1.41 (s, 9H); 2.62-3.20 (br m, 4H); 3.30-3.40 (m, 1H); 3.72-4.44 (br m, 4H); 4.72-4.98 (br m, 1H); 6.62-6.66 (br m, 1H); 7.25-7.63 (m, 6H); 7.83-7.93 (br m, 1H); 8.57-8.66 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at  $m/z$  542. Anal calcd for C<sub>28</sub>H<sub>35</sub>N<sub>3</sub>S<sub>1</sub>O<sub>6</sub>·0.21C<sub>6</sub>H<sub>14</sub>: C, 62.78; H, 6.83; N, 7.51. Found: C, 62.65; H, 6.99; N, 7.36.

15

Example 135

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-formylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300MHz)  $\delta$  1.14 (d,  $J = 7.1$  Hz, 6H); 3.30-3.38 (m, 1H); 3.38-3.77 (br m, 8H); 6.64 (d,  $J = 8.5$  Hz, 1H); 7.34-7.62 (m, 6H); 7.88-7.92 (dd,  $J = 8.5, 1.7$  Hz, 1H); 8.08 (s, 1H); 8.65 (d,  $J = 1.7$  Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at  $m/z$  440.

Anal calcd for  $C_{23}H_{25}N_3S_1O_4$ : C, 62.85; H, 5.73; N, 9.56. Found: C, 63.05; H, 5.98; N, 9.47.

### Example 136

5 (2-Isopropylphenyl)[2-nitro-4-(E-((2-hydroxymethyl-4-tert-butoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.  $^1H$  NMR (DMSO- $d_6$ , 300MHz)  $\delta$  1.14 (d, J = 6.8 Hz, 6H); 1.41 (s, 9H); 2.72-3.50 (br m, 4H); 3.30-3.40 (m, 1H); 3.85-4.52 (br m, 4H); 4.74-4.91 (br m, 1H); 6.62-6.66 (br m, 1H); 7.28-7.62 (m, 6H); 7.81-7.91 (br m, 1H); 8.57-8.66 (br m, 1H). MS (APCI) (M+H) $^+$  at m/z 542. Anal calcd for  $C_{28}H_{35}N_3S_1O_6 \cdot 0.17C_6H_{14}$ : C, 62.65; H, 6.77; N, 7.55. Found: C, 62.54; H, 6.83; N, 7.33.

### Example 137

15 (2-Ethoxyphenyl)-[2-chloro-4-(E-((3-ethoxycarbonylpiperidin-1-yl)carbonyl)ethenyl) phenyl]sulfide

Sub  
A37

The title compound was prepared according to the procedures of Example 97.  $^1H$  NMR (CDCl $_3$ , 300 MHz)  $\delta$  1.25 (t, J= 7 Hz, 6H), broad peaks totaling 9 protons at 1.50-1.62, 1.65-1.92, 2.01-2.15, 2.45-2.55, 2.95-3.05, 3.13-3.30, 3.55-3.68, 3.90-4.10, 4.05 (q, J=7Hz, 2H), 4.15 (q, J=7Hz, 2H), 6.84 (d, J=9Hz, 1H), 6.80-6.95 (broad, 1H), 6.94-6.99 (m, 2H), 7.18 (dd, J=9Hz, 2Hz, 1H), 7.34-7.41 (m, 2H), 7.52 (d, J=15Hz, 1H), 7.55 (d, J=2Hz, 1H). Anal Calcd. for

SJV  
A37

174

$C_{25}H_{28}ClNO_4S$ : C, 63.35; H, 5.95; N, 2.95. Found: C, 63.17; H, 6.02; N, 26.02; N,

2.81.

### Example 138

5

(3- Aminophenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 3-aminothiophenol. Yellow solid (2.9 mg, 5.6%);  $^1H$ -NMR ( $CDCl_3$ , 500 MHz)  $\delta$  2.20 (s, 3H), 3.60 (br, m, 2H), 3.77 (br, m, 6H), 4.03 (br, s, 2H), 6.85 (dd, J = 4, 16 Hz, 1H), 6.90 (m, 3H), 7.04 (d, J = 17 Hz, 1H), 7.30 (t, J = 16 Hz, 1H), 7.52 (d, J = 17 Hz, 1H), 7.68(d, J = 31 Hz, 1H), 8.44 (d, J = 4 Hz, 1H). MS (APCI)  $(M+H)^+$  at m/z 427. FAB High Resolution MS calculated m/z for  $C_{21}H_{23}N_4O_4S$   $(M+H)^+$ : 427.1440. Observed m/z: 427.1440.

15

### Example 139

(4-Aminophenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 4-aminothiophenol. Yellow solid (2.5 mg, 4.9%);  $^1H$ -NMR ( $CDCl_3$ , 500 MHz)  $\delta$  2.19 (s, 3H), 3.58 (br, m, 2H), 3.76 (br, m, 6H), 4.03 (br, s, 2H), 6.80 (m, 1H), 6.93 (m, 3H), 7.37 (m, 1H), 7.46 (d, J = 17 Hz, 1H), 7.67 (d, J = 31 Hz, 1H), 8.43 (d, J = 3 Hz, 1H). MS (APCI)  $(M+H)^+$  at m/z 427. FAB

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High Resolution MS calculated  $m/z$  for  $C_{21}H_{23}N_4O_4S$  ( $M+H$ )<sup>+</sup>: 427.1440. Observed  $m/z$ : 427.1441.

#### Example 140

5                    (2,4-Dimethylphenyl)[2- nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

10                    The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 2,4-dimethylthiophenol. Yellow solid (40 mg, 76%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 1.54 (br, s, 2H), 2.14 (s, 3H), 3.53 (br, m, 2H), 3.71 (br, m, 6H), 6.58 (d, J = 21 Hz, 1H), 6.76 (d, J = 38 Hz, 1H), 7.03 (m, 1H), 7.09 (m, 1H), 7.28 (br, d, J = 19 Hz, 1H), 7.33 (d, J = 20 Hz, 1H), 7.51 (d, J = 38 Hz, 1H), 8.30 (d, J = 5 Hz, 1H). MS (APCI) ( $M+H$ )<sup>+</sup> at  $m/z$  440. FAB High Resolution MS calculated  $m/z$  for  $C_{23}H_{26}N_3O_4S$  ( $M+H$ )<sup>+</sup>: 440.1644. Observed  $m/z$ : 440.1656.

15                    Example 141

(2,5-Dimethylphenyl)[2- nitro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

20                    The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 2,5-dimethylthiophenol. Yellow solid (34 mg, 64%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.07 (s, 3H), 2.23 (s, 3H), 2.28 (s, 3H), 3.46 (br, m, 2H), 3.64 (br, m, 6H), 6.65 (d, J = 21 Hz, 1H), 6.81 (d, J = 39 Hz, 1H), 7.19 (m, 2H), 7.34 (m, 2H), 7.56 (d, J = 38 Hz, 1H), 8.35 (d, J = 5 Hz, 1H). MS (APCI)

(M+H)<sup>+</sup> at m/z 440. FAB High Resolution MS calculated m/z for C<sub>23</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub>S

(M+H)<sup>+</sup>: 440.1644. Observed m/z: 440.1656.

#### Example 142

5                    (4-Methoxyphenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-  
yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 4-methoxythiophenol. Yellow solid (44 mg, 83%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.09 (s, 3H), 3.48 (br, m, 2H), 3.66 (br, m, 6H),  
10    3.83 (s, 3H), 6.79 (d, J = 22 Hz, 1H), 6.83 (d, J = 40 Hz, 1H), 6.95 (m, 1H), 6.98 (m, 1H), 7.37 (br, d, J = 20 Hz, 1H), 7.43 (m, 1H), 7.46 (m, 1H), 7.58 (d, J = 38 Hz, 1H), 8.35 (d, J = 4 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 442. FAB High Resolution MS calculated m/z for C<sub>22</sub>H<sub>24</sub>N<sub>3</sub>O<sub>5</sub>S (M+H)<sup>+</sup>: 442.1437. Observed m/z: 442.1434.

15                    Example 143

(3-Chlorophenyl)[2-nitro-4-( E-((4-acetylpiperazin-1-  
yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 83 substituting 3,4-dimethylthiophenol with 3-chlorothiophenol. Yellow solid (43 mg, 80%); <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 400 MHz) δ 2.23 (s, 3H), 3.62 (br, m, 2H), 3.80 (br, m, 6H),  
20    6.97 (d, J = 21 Hz, 1H), 6.99 (d, J = 39 Hz, 1H), 7.28 (d, J = 19 Hz, 1H), 7.57 (m, 3H), 7.675 (t, J = 4 Hz, 1H), 7.73 (d, J = 39 Hz, 1H), 8.48 (d, J = 4 Hz, 1H). FAB

High Resolution MS calculated  $m/z$  for  $C_{21}H_{21}N_3O_4ClS$  ( $M+H$ )<sup>+</sup>: 446.0941. Observed  $m/z$ : 446.0953.

Example 144

5      (2-Chloro, 4,5-diaminophenyl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Example 144A

10      (2-Chloro, 4-nitro, 5-aminophenyl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 65B substituting 2,3-dichlorobenzaldehyde with 4,5-dichloro-2-nitroaniline.

Example 144B

15      (2-Chloro, 4,5-diaminophenyl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

To a stirred solution of nitrobenzene from Example 144A (170 mg, 0.34 mmol) in 2 mL of EtOH was added  $SnCl_2$  (325 mg, 1.72 mmol). The mixture was then refluxed under nitrogen atmosphere for 2 h. The reaction was allowed to cool  
20 down to ambient temperature, quenched with sat.  $NaHCO_3$ , extracted with EtOAc(2×20 mL). The combined organic layer was washed with brine, dried over  $Na_2SO_4$ , concentrated in vacuo. The residue was then purified on Gilson preparative

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HPLC as described in Example 38B to give the title compound (70 mg, 44% yield) as a light yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.42-3.80 (m, 8H), 4.84 (s, 2H), 5.32 (s, 2H), 6.51 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 15.6 Hz, 1H), 7.41 (d, *J* = 15.6 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 1.8 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 465, 467, 469, 471.

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#### Example 145

(3,4-Diaminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

10 The title compound was prepared by the procedures described in Example 144, substituting 4,5-dichloronitroaniline with 5-chloronitroaniline, resulting in a light brown solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.31-3.80 (m, 8H), 4.75 (s, 2H), 5.01 (s, 2H), 6.61 (t, *J* = 4.2 Hz, 3H), 6.68 (s, 1H), 7.26 (d, *J* = 15.6 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.94 (s, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 431, 433.

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#### Example 146

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(6-Chlorobenzimidazol-2-on-5-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

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20 A mixture of dianiline from Example 144 (35 mg, 0.075 mmol) and CDI (13 mg, 0.075 mmol) in THF was stirred at ambient temperature for one day. Solvent was then removed under reduced pressure. The crude product then purified on a Gilson

preparative HPLC as described in Example 38B to give the title compound (12 mg, 32% yield) as a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.40-3.80 (m, 8H), 6.63 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.12 (s, 1H), 7.23 (s, 1H), 7.32 (d, *J* = 15.6 Hz, 1H), 7.43 (d, *J* = 15.6 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 8.03 (br s, 1H). MS (APCI<sup>+</sup>) (M-CO+H)<sup>+</sup> at *m/z* 465, 467.

#### Example 147

(1-Methylindol-7-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

10 The title compound was prepared by the procedures described in 85, substituting 5-iodoindole with *N*-methyl-7-bromoindole, giving a light brown solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.14 (s, 3H), 3.47-3.56 (m, 2H), 3.56-3.83 (m, 6H), 3.96 (s, 3H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.55 (d, *J* = 3.6 Hz, 1H), 6.76 (d, *J* = 15.6 Hz, 1H), 6.99 (d, *J* = 3.6 Hz, 1H), 7.09 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.15 (t, *J* = 7.65 Hz, 1H), 15 7.42 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.55 (dd, *J* = 15.6 Hz, 1H), 7.77 (dd, *J* = 0.9, 7.5 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 454, 456.

#### Example 148

(2-Hydroxy, 4-aminophenyl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

20 The title compound was prepared by the procedures described in Example 144, substituting 4,5-dichloronitroaniline with 5-chloronitrophenol, giving a light brown

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solid.  $^1\text{H}$  NMR ( $\text{d}^6\text{-DMSO}$ , 300 MHz)  $\delta$  2.04 (s, 3H), 3.41-3.80 (m, 8H), 5.09 (s, 2H), 6.61 (d,  $J = 8.4$  Hz, 1H), 6.70 (d,  $J = 7.8$  Hz, 1H), 6.79 (s, 1H), 6.80 (dd,  $J = 2.1, 7.8$  Hz, 1H), 7.26 (d,  $J = 15.6$  Hz, 1H), 7.40 (d,  $J = 15.6$  Hz, 1H), 7.46 (d,  $J = 8.4$  Hz, 1H), 7.94 (br s, 1H). MS (APCI $^+$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  432, 434.

5

#### Example 149

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl]  
sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

10  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 300MHz)  $\delta$  1.14 (d,  $J = 7.0$  Hz, 6H); 2.19 (s, 3H); 2.25-2.36 (br m, 4H); 3.30-3.40 (m, 1H); 3.51-3.72 (br m, 4H); 6.63 (d,  $J = 8.5$  Hz, 1H); 7.24-7.63 (m, 6H); 7.88-7.92 (dd,  $J = 8.8, 1.8$  Hz, 1H); 8.64 (d,  $J = 1.8$  Hz, 1H). MS (APCI) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  426. Anal calcd for  $\text{C}_{23}\text{H}_{27}\text{N}_3\text{S}_1\text{O}_3 \cdot 0.26\text{H}_2\text{O}$ : C, 64.19; H, 6.45; N, 9.76. Found: C, 64.21; H, 6.59; N, 9.70.

15

#### Example 150

(2-Isopropylphenyl)[2-nitro-4-(*E*-((4-(pyridine-2-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

20  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 300MHz)  $\delta$  1.14 (d,  $J = 6.8$  Hz, 6H); 3.30-3.40 (m, 1H); 3.51-3.83 (br m, 8H); 6.61-6.66 (br m, 1H); 7.30-7.65 (m, 8H); 7.83-7.97 (m, 2H); 8.57-

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8.67 (m, 2H). MS (APCI) (M+H)<sup>+</sup> at m/z 517. Anal calcd for C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>S<sub>1</sub>O<sub>4</sub>·0.45H<sub>2</sub>O: C, 64.07; H, 5.53; N, 10.67. Found: C, 64.04; H, 5.77; N, 10.97.

### Example 151

5      (2-Isopropylphenyl)[2-nitro-4-( E-((4-(pyridine-3-carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 3.30-3.40 (m, 1H); 3.52-3.87 (br m, 8H); 6.64 (d, J = 8.5 Hz, 1H); 7.30-7.64 (m, 7H); 7.83-7.95 (m, 2H); 8.61-10 8.70 (m, 3H). MS (APCI) (M+H)<sup>+</sup> at m/z 517. Anal calcd for C<sub>28</sub>H<sub>28</sub>N<sub>4</sub>S<sub>1</sub>O<sub>4</sub>·0.42H<sub>2</sub>O: C, 64.16; H, 5.55; N, 10.69. Found: C, 64.18; H, 5.64; N, 10.59.

### Example 152

15      (2-Isopropylphenyl)[2-nitro-4-( E-((2-carbomethoxy-4-methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.1 Hz, 6H); 2.70-3.95 (br m, 4H); 3.30-3.40 (m, 1H); 3.61, 3.61 (s, s, 3H); 3.65, 3.67 (s, s, 3H); 4.16-4.50 (br m, 2H); 5.08-5.39 (br m, 1H); 6.64 (dd, J = 8.5, 5.1 Hz, 1H); 7.30-7.63 (m, 6H); 7.83-7.94 (m, 1H); 20 8.62-8.67 (m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 528. Anal calcd for C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>7</sub>·0.19C<sub>6</sub>H<sub>14</sub>: C, 59.94; H, 5.87; N, 7.72. Found: C, 59.87; H, 5.94; N, 7.59.

Example 153

(2-Isopropylphenyl)[2-nitro-4-( E-((2-carboxy-4-methoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

5 Prepared according to the procedures of Example 71, giving a yellow solid.  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 2.70-3.95 (br m, 4H); 3.30-3.40 (m, 1H); 3.61, 3.61 (s, s, 3H); 4.16-4.51 (br m, 2H); 5.01-5.28 (br m, 1H); 6.61-6.66 (m, 1H); 7.30-7.63 (m, 6H); 7.83-7.94 (m, 1H); 8.66 (br s, 1H). MS (APCI) (M-H)<sup>+</sup> at m/z 512.

10

Example 154

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carbomethoxy-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 2.25, 2.26 (s, s, 3H); 2.20-3.98 (br m, 8H); 3.57, 3.63 (s, s, 3H); 6.63 (d, J = 8.5 Hz, 1H); 7.30-7.63 (m, 6H); 7.91 (dd, J = 8.5, 1.5 Hz, 1H); 8.60-8.68 (br m, 1H). MS (APCI) (M-H)<sup>+</sup> at m/z 484.

Example 155

20 (2-Ethoxyphenyl)-[2-chloro-4(E-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl]  
sulfide

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5 The compound of Example 137 was hydrolyzed using an excess of aqueous 10% NaOH in methanol, stirring overnight. The reaction mixture was concentrated in vacuo, water was added, and the solution was extracted with ether. The mixture was acidified; the resultant solid was collected by filtration and dried overnight in a vacuum oven, giving a white solid, m.p. 166-171C. <sup>1</sup>H-NMR (DMSO 300 MHz)  $\delta$  1.17 (t, J=7Hz, 3H), broad peaks totaling 9 protons at 1.32-1.48, 1.51-1.78, 1.90-2.04, 2.25-2.50, 2.80-2.90, 2.95-3.17, 3.45-3.51, 3.95-4.19, 4.41-4.51, 4.06 (q, J=7Hz, 1H), 6.80 (d, J=9Hz, 1H), 7.01 (t, J=7Hz, 1H), 7.15 (d, J=8Hz, 1H), 7.26-7.40 (m, 2H), 7.40-7.48 (m, 1H), 7.51 (dd, J=9Hz, 2Hz, 1H), 7.99 (d, J=9Hz, 1H). Anal. Calcd. for 10 C<sub>23</sub>H<sub>24</sub>ClNO<sub>4</sub>S: C, 61.94; H, 5.42; N, 3.14. Found: C, 61.75; H, 5.65; N, 3.15. The resultant acid (303 mg, 0.631 mmol) was dissolved in 3 ml MeOH. A KOH solution (38 mg, 0.595 mmol, of 87.6% KOH) in 1 ml MeOH was added. The resulting solution was concentrated in vacuo, and 5 ml. ether was added. The mixture was stirred for one hour to form a powder, which was filtered and dried in the vacuum 15 oven at 60C to yield 307 mg of a solid, water soluble product.

#### Example 155

(2-Ethoxyphenyl)-[2-chloro-4(E-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl]  
sulfide

20 The compound of Example 137 was hydrolyzed using an excess of aqueous 10% NaOH in methanol, stirring overnight. The reaction mixture was concentrated *in vacuo*, water was added, and the solution was extracted with ether, giving a white

solid, m.p. 166-171.  $^1\text{H}$  NMR (DMSO, 300 MHz)  $\delta$  1.17 (t,  $J=7\text{Hz}$ , 3H), broad peaks totaling 9 protons at 1.32-1.48, 1.51-1.78, 1.90-2.04, 2.25-2.50, 2.80-2.90, 2.95-3.17, 3.45-3.51, 3.95-4.19, 4.41-4.51, 4.06 (q,  $J=7\text{Hz}$ , 1H), 6.80 (d,  $J=9\text{Hz}$ , 1H), 7.01 (t,  $J=7\text{Hz}$ , 1H), 7.15 (d,  $J=8\text{Hz}$ , 1H), 7.26-7.40 (m, 2H), 7.40-7.48 (m, 1H), 7.51 (dd,  $J=9\text{Hz}$ , 2H, 1H), 7.99 (d,  $J=9\text{Hz}$ , 1H). Anal. Calcd. for  $\text{C}_{23}\text{H}_{24}\text{ClNO}_4\text{S}$ : C, 61.94; H, 5.42; N, 3.14. Found: C, 61.75; H, 5.65; N, 3.15. The resultant acid (303 mg, 0.631 mmol) was dissolved in 3 ml MeOH. A KOH solution (38 mg, 0.595 mmol, of 87.6% KOH) in 1 ml MeOH was added. The resulting solution was concentrated in vacuo, and 5 ml. ether was added. The mixture was stirred for one hour to form a powder, which was filtered and dried in the vacuum oven at 60C to yield 307 mg of a solid, water soluble product.

Example 156

(2-Ethoxyphenyl)-[2-chloro-4-(E-[(2-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl)phenyl]sulfide

The title compound was prepared according to the procedures of Example 97.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.24 (t,  $J=7\text{Hz}$ , 3H), 1.28 (t,  $J=7\text{Hz}$ , 3H), broad peaks totaling 9 protons at 1.35-1.55, 1.65-1.80, 2.25-2.38, 3.33-3.45, 3.95-4.05, 4.15-4.28, 4.60-4.80, 5.44-5.50, 4.05 (q,  $J=7\text{Hz}$ , 2H), 4.20 (q,  $J=7\text{Hz}$ , 2H), 6.80-6.98 (m, 4H), 7.12-7.20 (m, 1H) 7.35-7.43 (m, 2H), 7.50-7.58 (m, 2H). Anal. Calcd. for  $\text{C}_{25}\text{H}_{28}\text{ClNO}_4\text{S}$ : C, 63.35; H, 5.95; N, 2.95. Found: C, 63.51; H, 6.22; N, 2.61.

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A44Example 159

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(E-(((pyrrol-3-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.81 (s, 1H), 7.68 (d, 1H, J = 15.4 Hz), 7.35-7.47 (m, 3H), 7.04 (d, 1H, J = 8.4 Hz), 6.97 (dd, 1H, J = 1.3, 7.5 Hz), 6.91 (d, 1H, J = 8.5 Hz), 6.70 (d, 1H, J = 15.4 Hz), 5.94 (m, 1H), 5.85 (m, 1H), 4.47 (br, 2H), 4.38 (br, 2H), 3.98 (q, 2H, J = 7.0 Hz), 1.19 (t, 3H, J = 7.0 Hz). MS (ESI) *m/z* 420, 839, 861.

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Sub<sup>10</sup>  
A45Example 160

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-  
ylamino)carbonyl) ethenyl)phenyl]sulfide

The title compound was prepared according to the procedures of Example 1.

- 15 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.78 (s, 1H), 7.54 (d, 1H, J = 15.8 Hz), 7.42 (dd, 1H, J = 1.7, 7.5 Hz), 7.34-7.39 (m, 2H), 7.13 (br, 1H), 7.03 (d, 1H, J = 8.5), 6.97 (dd, 1H, J = 1.1, 7.7 Hz), 6.91 (d, 1H, J = 8.1 Hz), 6.46 (d, 1H, J = 15.8 Hz), 3.98 (q, 2H, J = 7.0 Hz), 3.43 (m, 4H), 3.34 (q, 2H, J = 6.0 Hz), 2.45 (t, 2H, J = 8.1 Hz), 2.08 (m, 2H), 1.75 (m, 2H), 1.18 (t, 3H, J = 7.0 Hz). MS (ESI) *m/z* 493, 515, 985, 1007.

20

Example 161

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.79 (s, 1H), 7.62 (d, 1H, J = 15.6 Hz), 7.44 (dd, 1H, J = 1.7, 7.5 Hz), 7.38 (m, 2H), 7.04 (d, 1H, J = 8.1), 6.97 (dd, 1H, J = 1.4, 7.5 Hz), 6.92 (d, 1H, J = 8.1 Hz), 6.84 (d, 1H, J = 15.6 Hz), 3.98 (q, 2H, J = 7.0 Hz), 3.63-78 (m, 5 6H), 3.53 (m, 2H), 2.14 (s, 3H), 1.19 (t, 3H, J = 7.0 Hz). MS (ESI) *m/z* 479, 501, 957, 979.

#### Example 162

10 (2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-(ethoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 71.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.79 (d, 1H, J = 1.7 Hz), 7.63 (d, 1H, J = 15.3 Hz), 7.43 (dd, 1H, J = 1.7, 7.7 Hz), 7.38 (m, 2H), 7.04 (d, 1H, J = 8.5), 6.97 (dd, 1H, J = 1.4, 7.5 Hz), 6.92 (d, 1H, J = 8.1 Hz), 6.84 (d, 1H, J = 15.3 Hz), 4.18 (q, 2H, J = 7.1 15 Hz), 3.98 (q, 2H, J = 6.9 Hz), 3.68 (m, 4H), 3.53 (m, 4H), 1.29 (t, 3H, J = 7.1 Hz) 1.19 (t, 3H, J = 6.9 Hz). MS (ESI) *m/z* 509, 531, 1017, 1039.

#### Example 163

20 (2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((4-(2-furylcarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 71.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.80 (d, 1H, J = 1.5 Hz), 7.66 (d, 1H, J = 15.4 Hz),

7.52 (s, 1H), 7.45 (dd, 1H,  $J = 1.6, 7.5$  Hz), 7.40 (m, 2H), 7.08 (d, 1H,  $J = 4.0$  Hz), 7.04 (d, 1H,  $J = 8.1$ ), 6.98 (dd, 1H,  $J = 1.1, 7.3$  Hz), 6.93 (d, 1H,  $J = 8.5$  Hz), 6.88 (d, 1H,  $J = 15.4$  Hz), 6.52 (dd, 1H,  $J = 1.6, 3.5$  Hz), 3.98 (q, 2H,  $J = 7.0$  Hz), 3.73-3.90 (m, 8H), 1.19 (t, 3H,  $J = 7.0$  Hz). MS (ESI)  $m/z$  531, 553, 1061, 1083.

5

Example 164

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(3-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl)phenyl]sulfide

The title compound was prepared according to the procedures of Example 97.

- 10  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J=7\text{Hz}$ , 6H), broad peaks totaling 9 protons at 1.65-1.80, 1.95-2.04, 2.51-2.63, 2.90-3.00, 3.15-3.30, 2.95-4.05, 4.42-4.55, 4.14 (q,  $J=7\text{Hz}$ , 2H), 4.15 (q,  $J=7\text{Hz}$ , 2H), 6.82 (d,  $J=15$  Hz, 1H), 6.84 (d,  $J=9\text{Hz}$ , 1H), 6.93-6.99 (m, 2H), 7.17 (dd,  $J=9\text{Hz}, 2\text{Hz}$ , 1H), 7.34-7.41 (m, 2H), 7.52 (d,  $J=15\text{Hz}$ , 1H), 7.55 (d,  $J=2\text{Hz}$ , 1H). Anal. Calcd. for  $\text{C}_{25}\text{H}_{28}\text{ClNO}_4\text{S}$ : C, 63.35; H, 5.95; N, 2.95. Found: C, 63.09; H, 6.24; N, 2.77.
- 15

Example 165

(2-Ethoxyphenyl)-[2-chloro-4(*E*-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl]sulfide

20

The compound of Example 164 was hydrolyzed, and the salt formed, according to the procedures of Example 155. m.p. 165-166C.  $^1\text{H-NMR}$  (DMSO 300 MHz)  $\delta$  1.25 (t,  $J=7\text{Hz}$ , 3H), 1.35-1.58 (m, 2H), 1.80-1.95 (m, 2H), 2.50-2.60 (m,

1H), 1.78-1.91 (m, 1H), 3.13-3.24 (m, 1H), 4.05 (q, J=7Hz, 2H), 4.12-4.35 (m, 2H), 6.80 (d, J=9Hz, 1H), 6.96-7.05 (t, J=8 Hz, 1H), 7.15 (d, J=9Hz, 1H), 7.28-7.48 (m, 4H), 7.51 (dd, J=9Hz, 2Hz, 1H), 8.00 (d, J=2Hz).

5

Example 166

(Benzodioxan-6-yl)[2-chloro-4-( E-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl] phenyl]  
sulfide

The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 6-iodobenzenedioxane, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.14 (s, 3H), 3.44-3.57 (m, 2H), 3.57-3.86 (m, 6H), 4.25-4.35 (m, 4H), 6.75 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 15.6 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 2.1, 8.4 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 7.18 (dd, J = 2.1, 8.4 Hz, 1H), 7.51 (d, J = 2.1 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at m/z 459, 461.

15

Example 167

(2-Isopropylphenyl)[2-nitro-4-( E-((4-ethoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl]  
phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 1.19 ( t, J = 7.0Hz, 3H); 3.30-3.40 (m, 1H); 3.30-3.73 (br m, 8H); 4.06 ( q, J = 7.0 Hz, 2H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.63 (m, 6H); 7.90 (dd, J = 8.8, 1.8 Hz, 1H); 8.65 (d, J = 1.8 Hz, 1H). MS

(APCI) (M+H)<sup>+</sup> at m/z 484. Anal calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>: C, 62.09; H, 6.04; N, 8.69.

Found: C, 61.89; H, 6.13; N, 8.51.

#### Example 168

5        (2-Isopropylphenyl)[2-nitro-4-( E-((4-isopropoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.20 (d, J = 6.4 Hz, 3H);  
3.30-3.40 (m, 1H); 3.32-3.73 (br m, 8H); 4.79 (hept, J = 6.1 Hz, 2H); 6.64 (d, J = 8.5  
10 Hz, 1H); 7.32-7.63 (m, 6H); 7.89 (dd, J = 8.5, 1.7 Hz, 1H); 8.64 (d, J = 1.7 Hz, 1H).  
MS (APCI) (M+H)<sup>+</sup> at m/z 498. Anal calcd for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>: C, 62.76; H, 6.28; N,  
8.44. Found: C, 62.57; H, 6.43; N, 8.33.

#### Example 169

15        (2-Isopropylphenyl)[2-nitro-4-( E-((4-isobutoxycarbonylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 0.90 (d, J = 6.6 Hz, 6H); 1.14 (d, J = 7.0 Hz, 6H);  
1.88 (hept, J = 6.6 Hz, 1H); 3.30-3.40 (m, 1H); 3.30-3.73 (br m, 8H); 3.81 (d, J = 6.3  
20 Hz, 2H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.63 (m, 6H); 7.90 (dd, J = 8.5, 1.5 Hz, 1H);  
8.65 (d, J = 1.5 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 512. Anal calcd for  
C<sub>27</sub>H<sub>33</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>: C, 63.38; H, 6.50; N, 8.21. Found: C, 63.15; H, 6.55; N, 8.13.

Example 170

(2-Isopropylphenyl)[2-nitro-4-( E-((4-((1-propen-2-oxy)carbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

5 Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.88 (s, 3H); 3.30-3.40 (m, 1H); 3.30-3.78 (br m, 8H); 4.65 (s, 1H); 4.69 (m, 1H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.63 (m, 6H); 7.90 (dd, J = 8.5, 1.5 Hz, 1H); 8.65 (d, J = 1.5 Hz, 1H). MS (APCI) (M+NH<sub>4</sub>)<sup>+</sup> at m/z 513. Anal calcd for C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>: C, 63.01; H, 5.90; N, 8.48.

10 Found: C, 62.98; H, 6.06; N, 8.27.

Example 171

(2-Isopropylphenyl)[2-nitro-4-( E-((4-propionylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

15 Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.00 (t, J = 7.3 Hz, 3H); 1.14 (d, J = 7.0 Hz, 6H); 2.35 (q, J = 7.5 Hz, 2H); 3.30-3.40 (m, 1H); 3.41-3.76 (br m, 8H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.63 (m, 6H); 7.90 (dd, J = 8.5, 1.5 Hz, 1H); 8.64 (d, J = 1.5 Hz, 1H). MS (APCI) (M+ NH<sub>4</sub>)<sup>+</sup> at m/z 485. Anal calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>4</sub>: C, 64.22; H, 6.25; N,

20 8.99. Found: C, 64.04; H, 6.44; N, 8.80.

Example 172

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(2-Isopropylphenyl)[2-nitro-4-( E-((4-carboxamidopiperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 3.30-3.40 (m, 1H); 3.30-  
5 3.73 (br m, 8H); 6.10 (s, 2H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.63 (m, 6H); 7.91 (dd, J  
= 8.5, 1.8 Hz, 1H); 8.65 (d, J = 1.8 Hz, 1H). MS (APCI) (M+ NH<sub>2</sub>)<sup>+</sup> at m/z 470. Anal  
calcd for C<sub>23</sub>H<sub>26</sub>N<sub>4</sub>S<sub>1</sub>O<sub>4</sub>·0.26CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 60.48; H, 5.93; N, 11.73. Found: C,  
60.10; H, 5.84; N, 11.90.

Example 173

(2-Isopropylphenyl)[2-nitro-4-( E-((4-methylaminocarbonylpiperazin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 2.58 (d, J = 4.4 Hz, 3H);  
15 3.30-3.40 (m, 1H); 3.28-3.70 (br m, 8H); 6.52 (q, J = 4.4 Hz, 1H); 6.64 (d, J = 8.5 Hz,  
1H); 7.32-7.62 (m, 6H); 7.90 (dd, J = 8.5, 1.8 Hz, 1H); 8.64 (d, J = 1.8 Hz, 1H). MS  
(APCI) (M+NH<sub>4</sub>)<sup>+</sup> at m/z 486. Anal calcd for C<sub>24</sub>H<sub>28</sub>N<sub>4</sub>S<sub>1</sub>O<sub>4</sub>·0.36CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C,  
61.07; H, 6.22; N, 11.19. Found: C, 61.14; H, 6.41; N, 11.19.

Example 174

(2-Isopropylphenyl)[2-nitro-4-( E-((4-(pyrimidin-2-yl)piperazin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide

0054795-033100  
0054795-033100

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.15 (d, J = 6.6 Hz, 6H); 3.30-3.40 (m, 1H); 3.28-3.85 (br m, 8H); 6.64 (d, J = 8.5 Hz, 1H); 6.68 (d, J = 4.8 Hz, 1H); 7.33-7.63 (m, 6H); 7.92 (dd, J = 8.5, 1.8 Hz, 1H); 8.40 (d, J = 4.8 Hz, 2H); 8.67 (d, J = 1.8 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 490. Anal calcd for C<sub>26</sub>H<sub>27</sub>N<sub>3</sub>S<sub>1</sub>O<sub>3</sub>: C, 63.78; H, 5.56; N, 14.30. Found: C, 63.83; H, 5.54; N, 14.11.

#### Example 175

(2-Isopropylphenyl)[2-nitro-4-( E-((4-hydroxyacetyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.15 (d, J = 6.8 Hz, 6H); 3.30-3.40 (m, 1H); 3.28-3.78 (br m, 8H); 4.12 (d, J = 5.8 Hz, 2H); 4.61-4.69 (br m, 1H); 6.64 (d, J = 8.5 Hz, 1H); 7.33-7.63 (m, 6H); 7.90 (dd, J = 8.5, 1.8 Hz, 1H); 8.65 (d, J = 1.8 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 470. Anal calcd for C<sub>24</sub>H<sub>27</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>·0.38CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 60.93; H, 6.02; N, 8.35. Found: C, 60.95; H, 6.06; N, 8.35.

#### Example 176

(2-Isopropylphenyl)[2-nitro-4-( E-((4-(pyrazine-2-carbonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 3.30-3.40 (m, 1H); 3.28-

3.88 (br m, 8H); 6.61-6.66 (br m, 1H); 7.31-7.63 (m, 6H); 7.85-7.96 (br m, 1H); 8.61-8.92 (m, 4H). MS (APCI) (M+H)<sup>+</sup> at m/z 518. Anal calcd for C<sub>27</sub>H<sub>27</sub>N<sub>5</sub>S<sub>1</sub>O<sub>4</sub>·0.24CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 62.34; H, 5.41; N, 13.01. Found: C, 62.23; H, 5.50; N, 13.10.

5

Sub  
48Example 177

(2-Isopropylphenyl)[2-trifluoromethyl-4-( E-(((2-carboxypyrrol-3-in-1-yl)carbonyl)ethenyl)-phenyl] sulfide

The title compound was prepared according to the procedures of Example 71.

- 10 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.79 (s, 1H), 7.68 (d, 1H, J = 15.4 Hz), 7.48 (d, 1H, J = 7.4 Hz), 7.45 (m, 2H), 7.38 (d, 1H, J = 8.3 Hz), 7.23 (m, 1H), 6.80 (d, 1H, J = 8.5 Hz), 6.70 (d, 1H, J = 15.4 Hz), 6.04 (m, 1H), 5.88 (m, 1H), 5.31 (m, 1H), 4.60 (m, 1H), 4.50 (m, 1H), 3.76 (s, 3H), 3.50 (m, 1H), 1.22 (d, 6H, J = 7.0 Hz). MS (ESI) m/z 476, 498, 951, 973. Anal. Calcd for C<sub>25</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>3</sub>S · 0.38 EtOAc: C, 62.58; H, 5.35; N, 2.75. Found: C, 62.53; H, 5.27; N, 2.76.
- 15

Example 178

(2-Isopropylphenyl)[2-nitro-4-( E-((3-hydroxymethyl-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 2.22 (s, 3H); 1.82-4.63 (br

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m, 9H); 3.30-3.40 (m, 1H); 6.62-6.66 (br m, 1H); 7.25-7.63 (m, 6H); 7.86-7.92 (br m, 1H); 8.57-8.65 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 456.

Example 179

5 (2-Isopropylphenyl)[2-trifluoromethyl-4-( E-(((2-carboxypyrrol-3-in-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.79 (s, 1H), 7.72 (d, 1H, J = 15.5 Hz), 7.49 (d, 1H, J = 7.4 Hz), 7.36-7.46 (m, 3H), 7.23 (m, 1H), 6.82 (d, 1H, J = 8.5 Hz), 6.74 (d, 1H, J = 15.4 Hz), 6.00 (br, 2H), 4.48 (br, 1H), 4.51 (br, 2H), 3.48 (m, 1H), 1.18 (d, 6H, J = 7.0 Hz). MS (ESI) m/z -460, -492, -921.

Example 180

15 (2-Isopropylphenyl)[2-trifluoromethyl-4-( E-(((2-hydroxymethylpyrrolidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.79 (s, 1H), 7.68 (d, 1H, J = 15.4 Hz), 7.48 (d, 1H, J = 7.4 Hz), 7.45 (m, 2H), 7.38 (d, 1H, J = 8.3 Hz), 7.23 (m, 1H), 6.80 (d, 1H, J = 8.5 Hz), 6.70 (d, 1H, J = 15.4 Hz), 5.82 (m, 1H), 5.70 (m, 1H), 4.92 (m, 1H), 4.18 (br s, 2H), 3.76 (s, 3H), 3.78 (d, 1H, J = 11.5 Hz), 3.50 (m, 2H), 3.01 (t, 2H, J = 7.5 Hz), 2.58 (t, 2H, J = 7.6 Hz), 1.19 (d, 6H, J = 7.1 Hz). MS (ESI) m/z 450, 472, 921.

Example 181

(2-Isopropylphenyl)[2-nitro-4-( E-((3-methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

5 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 2.60 (d, J = 4.4 Hz, 3H); 2.50-4.45 (br m, 7H); 3.30-3.40 (m, 1H); 6.62-6.66 (br m, 1H); 7.32-7.62 (m, 6H); 7.81-7.92 (m, 2H); 8.59-8.65 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 469.

Example 182

10 (2-Isopropylphenyl)[2-nitro-4-( E-(((3-cyclopropylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 0.40-0.62 (br m, 4H); 1.14 (d, J = 6.8 Hz, 6H); 2.50-4.41 (br m, 8H); 3.30-3.40 (m, 1H); 6.62-6.67 (br m, 1H); 7.32-7.62 (m, 6H); 7.87-15 7.92 (m, 2H); 8.59-8.64 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 495.

Example 183

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carboxamidopiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20 Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 2.50-4.42 (br m, 7H); 3.30-

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3.40 (m, 1H); 6.62-6.67 (br m, 1H); 7.12-7.62 (m, 8H); 7.87-7.92 (m, 1H); 8.60-8.65 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 455.

#### Example 184

5        (2-Isopropylphenyl)[2-nitro-4-( E-((3-carbomethoxy-4-oxopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 2.32-2.55 (br m, 2H); 3.30-3.40 (m, 1H); 3.64, 3.76 (s, s, 3H); 3.68-4.58 (br m, 5H); 6.64 (d, J = 8.5 Hz, 1H);  
10    7.32-7.63 (m, 6H); 7.88-7.96 (m, 1H); 8.60-8.68 (m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 483. Anal calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>S<sub>1</sub>O<sub>6</sub>·0.17C<sub>6</sub>H<sub>14</sub>: C, 62.86; H, 5.75; N, 5.63. Found: C, 62.81; H, 5.83; N, 5.60.

#### Example 185

15        (2-Isopropylphenyl)[2-nitro-4-( E-((3,5-dimethylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H

NMR (DMSO-d<sub>6</sub>, 300MHz) δ 0.96-1.06 (m, 6H); 1.14 (d, J = 6.8Hz, 6H); 2.07-4.39 (br m, 7H); 6.63 (d, J = 8.5 Hz, 1H); 7.30-7.63 (m, 6H); 7.92 (dd, J = 8.5, 1.7 Hz, 1H);  
20    8.60 (d, J = 1.7 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 440. Anal calcd for C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>3</sub>: C, 65.58; H, 6.65; N, 9.56. Found: C, 65.36; H, 6.87; N, 9.27.

00541795.033100  
007E0.5674560

The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with *N*-ethyl-7-bromoindole. white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.30 (t, *J* = 7.05 Hz, 3H), 2.14 (s, 3H), 3.52 (br s, 2H), 3.58-3.84 (m, 6H), 4.42 (q, *J* = 7.05 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 3.0 Hz, 1H), 6.76 (d, *J* = 15.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 3.0 Hz, 1H), 7.16 (t, *J* = 7.65 Hz, 1H), 7.42 (dd, *J* = 0.9, 7.5 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.78 (dd, *J* = 0.9, 7.5 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 468, 470.

Sub  
ASO

15 The title compound was prepared according to the procedures of Example 85.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.45 (s, 3H), 3.65-3.80 (m, 10H), 4.09-4.13 (m, 2H), 6.82 (broad d, J=15, 1H), 6.88 (d, J=9Hz, 1H), 6.87 (dd, J=9Hz, 2Hz, 1H), 7.03-7.10 (m, 2H), 7.20 (d, J=9Hz, 1H), 7.31 (t, J=8 Hz, 1H), 7.52 (s, 1H), 7.56 (broad d, J=15, 1H).

Example 188

(2-Bromophenyl)[2-chloro-4-(E-((4,4'-S-dioxythiomorpholin-1-yl)carbonyl)ethenyl)phenyl]sulfide

Sub  
AS1

4-Methylmorpholine *N*-oxide (0.0935 g, 0.798 mmol) and 4Å molecular  
5 sieves (0.0333g) were added to a solution of (2-Bromophenyl)[2-chloro-4-(E-  
(((thiomorpholin-1-yl)carbonyl) ethenyl)phenyl]sulfide (0.1230g, 0.27 mmol; prepared  
according to the procedures described in Example 1). After 15 min,  
tetrapropylammonium perruthenate (0.0058g, 0.0166 mmol) was added and after 4h  
had elapsed the starting material was consumed by TLC and the crude products were  
10 passed through a plug of silica with 5:2 hexane:ethyl acetate→ 9:1 CH<sub>2</sub>Cl<sub>2</sub>: MeOH.  
The mixture was then purified by preparative HPLC to provide the title compound  
(0.0138 g, 10%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.12 (d, *J* = 1.47 Hz, 1H), 7.81  
(dd, *J* = 7.9, 1.3, 2H), 7.65 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.27-  
7.53 (m, 4H), 7.03 (d, *J* = 9.0 Hz, 1H), 4.12 (br s, 2H), 3.98 (br s, 2H), 3.26 (br s, 2H),  
15 3.19 (br s, 2H), 1.54-2.29 (m, 6H), MS(APCI) (M+H)<sup>+</sup> at m/z 486, 488, 490.

Example 189

(2-Bromophenyl)[2-chloro-4-(E-(N-carbomethoxymethyl-N-(3-(pyrrolidin-2-on-1-yl)prop-1-yl)amino)carbonyl)ethenyl)phenyl]sulfide

20

Example 189A

N-Carbomethoxymethyl-N-(3-(pyrrolidin-2-on-1-yl)prop-1-yl)amine

00541795.033100

Methyl bromoacetate (1.35 mL, 14.3 mmol) was added dropwise to a solution of 3-aminopropyl-2-pyrrolidinone (2.0 mL, 14.3 mmol) and diisopropylethylamine (2.7 mL) in CH<sub>2</sub>Cl<sub>2</sub>. The reaction was stirred for 12h and was then concentrated *in vacuo*, and carried forward without further purification.

### Example 189B

(2-Bromophenyl)[2-chloro-4-(E-(N-carbomethoxymethyl-N-(3-(pyrrolidin-2-on-1-yl)prop-1-yl)amino)carbonyl) ethenyl]phenyl]sulfide

The title compound was prepared by the procedures described for Example 113, substituting 2,4 dichlorothiophenol with 2-bromothiophenol, 2-chlorobenzaldehyde with 3,4 dichlorobenzaldehyde, and 1-(3-aminopropyl)-5-((S)-hydroxymethyl)-2-pyrrolidinone with the compound from Example 189A. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.07 (dd, *J* = 9.4, 1.7 Hz, 1H), 7.81 (m, 1H), 7.64 (m, 1H), 7.24-7.49 (m, 5H), 7.05 (m, 1H), 4.53 (s, 1H), 4.14 (s, 1H), 3.68 (s, 1H), 3.64 (s, 2H), 3.54 (m, 2H), 3.13-3.43 (m, 4H), 2.39 (m, 2H), 1.91 (m, 2H), 1.72 (m, 2H), MS(APCI) (M+H)<sup>+</sup> at *m/z* 565, 567, 569.

### Example 190

(2-Bromophenyl)[2-chloro-4-(E-((4-S-oxythiomorpholin-1-yl)-2-pyrrolidinone)carbonyl) ethenyl]phenyl]sulfide

The title compound (0.0178g, 14%) was isolated from the same reaction mixture as described in Example 188. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300MHz) δ 8.12 (d, *J* =

Sub  
AS1

007EEO" 564TH560

Sub  
51

1.8 Hz, 1H), 7.81 (dd,  $J = 7.9, 1.3$  Hz, 1H), 7.65 (dd,  $J = 8.3, 1.7$  Hz, 1H), 7.46 (d,  $J = 7.4$  Hz, 1H), 7.26-7.48 (m, 4H), 7.04 (d,  $J = 7.4$  Hz, 1H), 4.29 (br m, 2H), 3.97 (br m, 1H), 3.61 (br m, 1H), 2.80 (br m, 4H), MS(APCI)  $(M+H)^+$  at  $m/z$  470, 472, 474.

5

Example 191

(2-Methoxy-5-chlorophenyl)[2-nitro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.44 (s, 1H), 7.66 (d, 1H,  $J = 15.1$  Hz), 7.58 (d, 1H,  $J = 2.6$  Hz), 7.48 (dd, 1H,  $J = 2.6, 8.8$  Hz), 7.44 (m, 1H), 6.97 (d, 1H,  $J = 8.8$  Hz), 6.92 (d, 1H,  $J = 15.5$  Hz), 6.82 (d, 1H,  $J = 8.5$  Hz), 3.78 (s, 3H), 3.70 (m, 6H), 3.54 (m, 2H), 2.15 (s, 3H). MS (ESI)  $m/z$  476, 498, 951, 973. Anal. Calcd for C<sub>22</sub>H<sub>22</sub>ClN<sub>3</sub>O<sub>5</sub>S · 0.48 EtOAc: C, 55.44; H, 5.03; N, 8.11. Found: C, 54.36; H, 4.90; N, 8.50.

15

Example 192

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-acetoxymethyl)piperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz)  $\delta$  1.14 (d,  $J = 6.8$  Hz, 6H); 2.04 (s, 3H); 3.30-3.40 (m, 1H); 2.50-4.46 (br m, 9H); 6.64 (d,  $J = 8.8$  Hz, 1H); 7.30-7.62 (m, 6H); 7.87-7.93 (m, 1H); 8.58-8.63 (br m, 1H). MS (APCI)  $(M+H)^+$  at  $m/z$  484. Anal calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub> · 0.2H<sub>2</sub>O: C, 61.60; H, 6.09; N, 8.62. Found: C, 61.63; H, 6.21; N, 8.41.

Sub  
AS2Example 193

(2-Isopropylphenyl)[2-nitro-4-( E-((3,5-dimethyl-4acetyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

5 Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.00-1.20 (br m, 6H); 1.15 (d, J = 6.8Hz, 6H); 2.04 (s, 3H); 2.76-4.58 (br m, 7H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.63 (m, 6H); 7.94 (dd, J = 8.5, 1.8 Hz, 1H); 8.66 (d, J = 1.8 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 482. Anal calcd for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>S<sub>1</sub>O<sub>4</sub>·0.3H<sub>2</sub>O: C, 64.13; H, 6.54; N, 8.63. Found: C, 64.15; H, 6.61;

10 N, 8.50.

Example 194

(1-Methylindol-5-yl)[2-chloro-4-( E-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

15 The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with *N*-methyl-5-bromoindole, giving a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.40-3.80 (m, 8H), 3.86 (s, 3H), 6.49 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 3.0 Hz, 1H), 7.27 (d, J = 15.6 Hz, 1H), 7.31 (dd, J = 2.4, 8.4 Hz, 1H), 7.39 (d, J = 15.6 Hz, 1H), 7.41 (dd, J = 1.8, 8.4 Hz, 1H), 7.48 (d, J = 3.0 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 1.8 Hz, 1H), 7.99 (br s, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at m/z 454, 456.

20

00110" 56ZT4560

Example 195

(Benzodioxan-6-yl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl]  
sulfide

5

Example 195A6-Mercaptobenzodioxane

The title compound was prepared by the procedures described in Example 97A, substituting 2-ethoxybenzene with 6-iodobenzenedioxane.

10

Example 195B

(Benzodioxan-6-yl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl]  
sulfide

15

The title compound was prepared by the procedures described in Example 32, substituting 2,4-dichlorobenzenethiol with 6-mercaptobenzenedioxane, to give a light-yellow solid; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.41-3.80 (m, 8H), 4.28-4.38 (m, 4H), 6.86 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.10 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 15.6 Hz, 1H), 7.91 (dd, *J* = 1.8, 8.4 Hz, 1H), 8.62 (d, *J* = 1.8 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 470. Anal. Calcd for C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>S · 0.17 H<sub>2</sub>O: C, 58.46; H, 4.98; N, 8.89. Found: C, 58.47; H, 4.88; N, 8.78.

20

---

Example 196

Sub  
AS3

Sub  
53

(Benzodioxan-6-yl)[2-nitro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 32, substituting 2,4-dichlorobenzenethiol with 6-mercaptobenzenedioxane, and 1-

5 acetylpiperazine with 3-aminopropyl-1-pyrrolidin-2-one, giving a light-yellow solid.

<sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.64 (p, *J* = 7.2 Hz, 2H), 1.92 (p, *J* = 7.8 Hz, 2H), 2.21 (t, *J* = 7.8 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 3.19 (t, *J* = 7.2 Hz, 2H), 3.38-3.46 (overlapping t, *J* = 7.8 Hz, 2H), 4.27-4.37 (m, 4H), 6.70 (d, *J* = 15.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 15.6 Hz, 1H), 7.77 (dd, *J* = 2.1, 8.4 Hz, 1H), 8.16 (t, *J* = 6.0 Hz, 1H), 8.41 (d, *J* = 2.1 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 484. Anal. Calcd for C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>S · 0.51 CH<sub>2</sub>Cl<sub>2</sub> · 0.24 MeOH: C, 55.61; H, 5.09; N, 7.86. Found: C, 55.39; H, 5.48; N, 8.26.

15

#### Example 197

(Benzodioxan-6-yl)[2-nitro-4-(E-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 196 substituting N-(3'-aminopropyl)-2-pyrrolidinone with ethyl nipecotate, giving a

20 yellow solid, mp 73-75 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.26 (t, *J* = 7.0 Hz, 3H), 1.74 (br, 1H), 1.78 (br, 1H), 2.10 (br, 1H), 2.54 (br, 1H), 2.95-3.70 (br, 2H), 3.90-4.10 (br, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.30-4.40 (m, 4H), 4.65 (br, 1H), 6.90 (d, *J* = 8.5 Hz,

1H), 6.98 (d, J=8.5 Hz, 1H), 7.06 (dd, J=2.0, 8.0 Hz, 1H), 7.10 (d, J=2.0 Hz, 1H), 7.40-7.50 (m, 1H), 7.58 (d, J=15.0 Hz, 1H), 8.40 (d, J=2.0 Hz, 1H). MS (APCI) m/z 499 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>S: C, 60.23; H, 5.26; N, 5.62. Found: C, 60.09; H, 5.43; N, 5.47.

5

#### Example 198

(Benzodioxan-6-yl)[2-nitro-4-( E-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedure described as in example 10 196 substituting N-(3'-aminopropyl)-2-pyrrolidinone with ethyl isonipecotate, giving a yellow solid, mp 78-88 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.27 (t, J=7.0 Hz, 3H), 1.65 (m, 2H), 2.00 (m, 2H), 2.60 (m, 1H), 2.80-3.50 (br, 2H), 4.15 (br, 1H), 4.16 (q, J=7.0, 2H), 4.34 (m, 4H), 4.54 (br, 1H), 6.90 (d, J=8.0 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.05 (dd, J=2.0, 8.0 Hz, 1H), 7.10 (d, J=2.0 Hz, 1H), 7.12 (br, 1H), 7.44 (d, J=8.0 15 Hz, 1H), 7.60 (br, 1H), 8.40 (s, 1H). MS (CI/NH<sub>3</sub>) m/z 499 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>S 0.03 H<sub>2</sub>O: C, 60.16; H, 5.26; N, 5.61. Found: C, 60.15; H, 5.65; N, 5.40.

#### Example 199

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(Z-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20

#### Example 199A

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(Z-((4-carbomethoxyethenyl) phenyl] sulfide

0044795 033100

Sub  
As4

Bis-(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (1.20 g, 3.77 mmole), and 18-crown-6 (3.56 g, 13.48 mmol) were dissolved in 22 ml of dry THF. The mixture was cooled to -78 °C and  $\text{KN}(\text{SiMe}_3)_2$  (0.5 M in THF, 4.04 mmol) was added and stirred for 30 min. (2-Ethoxyphenyl)[2-trifluoromethyl-4-formyl phenyl] sulfide (1.10 g, 3.77 mmol, prepared according to the procedure of example 1) in 13 ml of THF was added via cannulation. After 1 hr at that temperature, the cooling bath was removed and the mixture allowed to warm to ambient temperature. Saturated  $\text{NH}_4\text{Cl}$  soln. was added and the mixture was extracted with ethyl acetate three times. The combined organics were dried over sodium sulfate, concentrated *in vacuo* and purified by medium pressure chromatography on silica gel to give 772 mg (60% yield) of the cis- isomer ( $J_{\text{olefinic}} = 12.5 \text{ Hz}$ ) along with 322 mg (25% yield) of the trans- isomer ( $J_{\text{olefinic}} = 12.5 \text{ Hz}$ ).

#### Example 199B

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(Z-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl] phenyl] sulfide

The compound of Example 199A was converted to the corresponding amide according to the procedures of Example 1.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  7.64 (d, 1H,  $J = 16.9 \text{ Hz}$ ), 7.32-7.4 (m, 2H), 6.98 (m, 2H), 6.93 (m, 2H), 6.65 (d, 1H,  $J = 12.1 \text{ Hz}$ ), 6.08 (d, 1H,  $J = 12.2 \text{ Hz}$ ), 3.98 (q, 2H,  $J = 7.0 \text{ Hz}$ ), 3.68 (m, 2H), 3.62 (m, 2H), 3.44-3.54 (m, 4H), 2.11 and 2.05 (s, 3H), 1.20 (t, 3H,  $J = 7.0 \text{ Hz}$ ). MS (ESI)s  $m/z$  479, 501.

#### Example 200

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(E-((6-methylpyrid-2-ylamino)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.12 (d, 1H, J = 8.1 Hz), 7.78 (s, 1H, J = 1.7 Hz), 7.70 (d, 1H, J = 15.6 Hz), 7.63 (t, 1H, J = 7.8 Hz), 7.46 (dd, 1H, J = 1.6, 7.8 Hz), 7.36-7.42 (m, 2H), 7.04 (d, 1H, J = 8.1), 6.99 (dd, 1H, J = 1.2, 7.6 Hz), 6.92 (m, 2H), 6.50 (d, 1H, J = 15.6 Hz), 3.99 (q, 2H, J = 6.9 Hz), 2.47 (s, 3H), 1.19 (t, 3H, J = 7.0 Hz). MS (ESI)s *m/z* 459, 481. Anal. Calcd for C<sub>24</sub>H<sub>21</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S · 1.1 H<sub>2</sub>O: C, 60.27; H, 4.89; N, 5.86. Found: C, 60.28; H, 5.05; N, 5.94.

Example 201

(2-Methyl-3-chlorophenyl)[2-nitro-4-(E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.46 (d, 1H, J = 1.5 Hz), 7.64 (d, 1H, J = 15.4 Hz), 7.56 (d, 1H, J = 2.6 Hz), 7.54 (d, 1H, J = 2.2 Hz), 7.47 (d, 1H, J = 8.5 Hz), 7.27 (m, 1H), 6.92 (d, 1H, J = 15.4 Hz), 6.68 (d, 1H, J = 8.5 Hz), 3.63-3.78 (m, 6H), 3.53 (m, 2H), 2.45 (s, 3H), 2.15 (s, 3H). MS (ESI) *m/z* 460, 482, 919. Anal. Calcd for C<sub>22</sub>H<sub>22</sub>Cl<sub>1</sub>N<sub>3</sub>O<sub>4</sub>S: C, 57.45, H, 4.82, N, 9.14. Found: C, 75.54, 5.08, N, 8.82.

Example 202

(Benzodioxan-6-yl)[2-nitro-4-( E-((3-carboxamidopiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the procedures described in Example 196, substituting N-(3'-aminopropyl)-2-pyrrolidinone with nipecotamide, giving a light  
5 yellow solid, mp 243-245 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.38-1.50 (m, 2H), 1.77-2.00 (m, 2H), 2.38 (m, 1H), 2.70 (m, 1H), 3.11 (m, 1H), 4.22 (m, 1H), 4.28-4.30 (m, 2H), 4.32-4.36 (m, 2H), 4.42 (m, 1H), 6.85 (d, J=8.5 Hz, 1H), 7.04-7.16 (m, 2H), 7.35 (s, 1H), 7.40 (d, J=13.0 Hz, 1H), 7.48 (d, J=15.5 Hz, 1H), 7.91 (d, J=8.5 Hz, 1H), 8.58 (s, 1H). MS (APCI) m/z 470 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>S•0.37 H<sub>2</sub>O: C,  
10 58.01; H, 5.03; N, 8.82. Found: C, 58.02; H, 5.13; N, 8.61.

Example 203

(Benzodioxan-6-yl)[2-nitro-4-( E-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

15 The title compound was prepared by the procedures described in Example 196, substituting N-(3'-aminopropyl)-2-pyrrolidinone with ethyl pipecolate, producing a light yellow solid, mp 74-75 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.28 (t, J=7.0 Hz, 3H), 1.32-1.55 (m, 2H), 1.60-1.82 (m, 3H), 2.33 (m, 1H), 3.40 (m, 1H), 3.98 (m, 1H), 4.23 (q, J= 6.5 Hz, 2H), 4.32 (q, J=5.0 Hz, 4H), 5.45 (m, 1H), 6.90 (d, J=8.0 Hz, 1H),  
20 6.97 (d, J=8.0 Hz, 1H), 7.0-7.10 (m, 3H), 7.44 (d, J=7.5 Hz, 1H), 7.60 (d, J=15.0 Hz, 1H), 8.38 (m, 1H). MS (APCI) m/z 499 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>S•0.11 H<sub>2</sub>O: C, 59.99; H, 5.28; N, 5.60. Found: C, 59.98; H, 5.42; N, 5.91.

Example 204

(Benzodioxan-6-yl)[2-nitro-4-( E-((4-carboxamidopiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

5           The title compound was prepared by the procedures described in Example 196, substituting N-(3'-aminopropyl)-2-pyrrolidinone with isonipecotamide, giving a light yellow solid, mp >230 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 1.35 (m, 1H), 1.60 (m, 1H), 1.72 (m, 1H), 1.68 (m, 1H), 2.20 (m, 1H), 2.75 (m, 1H), 3.04 (m, 1H), 3.20 (m, 1H), 4.20 (m, 1H), 4.32 (m, 4H), 6.85 (d, J=8.5 Hz, 1H), 7.04 (d, J=8.5 Hz, 1H), 7.09 (dd, 10 J=2.0, 8.5 Hz, 1H), 7.26 (s, 1H), 7.37 (d, J=16.0 Hz, 1H), 7.47 (d, J=16.0 Hz, 1H), 8.58 (d, J=2.0 Hz, 1H). MS (APCI) m/z 470 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>6</sub>S•0.13 H<sub>2</sub>O: C, 58.55; H, 4.97; N, 8.91. Found: C, 58.41; H, 5.14; N, 9.30.

15

Example 205

(Benzodioxan-6-yl)[2-nitro-4-( E-((4-tert-butoxycarbonyl)piperazin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide

          The title compound was prepared by the procedures described in Example 196, substituting N-(3'-aminopropyl)-2-pyrrolidinone with Boc-piperazine, 20 giving a light yellow solid, mp 165-167 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.48 (s, 9H), 3.50 (m, 4H), 3.65 (br, m, 4H), 4.32 (m, 4H), 6.89 (d, J=5.0 Hz, 1H), 6.92 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 7.05 (dd, J=2.0, 8.5 Hz, 1H), 7.10 (d, J=2.0 Hz, 1H), 7.45

(m, 1H), 7.63 (d, J=15.5 Hz, 1H), 8.40 (m, 1H). MS (APCI) M/z 528 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>O<sub>7</sub>S: C, 59.19; H, 5.54; N, 7.96. Found: C, 58.85; H, 5.69; N, 8.20.

### Example 206

5      (2-Isopropylphenyl)[2-nitro-4-( E-((syn-3,5-dimethylmorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.10-1.18 (m, 12H); 2.29-2.39 (m, 1H); 2.67-2.78 (m, 1H); 3.30-3.53 (m, 3H); 4.17-4.38 (m, 2H); 6.63 (d, J = 8.8 Hz, 1H); 7.32-7.63 (m, 6H); 7.92 (dd, J = 8.8, 1.5 Hz, 1H); 8.66 (d, J = 1.8 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 441. Anal calcd for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>S<sub>1</sub>O<sub>4</sub>: C, 65.43; H, 6.41; N, 6.36. Found: C, 65.69; H, 6.70; N, 6.17.

### Example 207

15      (2-Isopropylphenyl)[2-nitro-4-( E-((anti-3,5-dimethylmorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.07-1.12 (m, 6H); 1.15 (d, J = 6.6 Hz, 6H); 3.32-3.48 (m, 3H); 3.60-3.83 (br m, 2H); 3.87-3.98 (m, 2H); 6.63 (d, J = 8.5 Hz, 1H); 7.32-7.63 (m, 6H); 7.93 (dd, J = 8.8, 1.8 Hz, 1H); 8.64 (d, J = 1.8 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 441.

Example 208

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carboethoxypiperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

5 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.08-1.26 (m, 3H); 2.52-3.16 (br m, 4H); 3.25-3.40 (m, 1H); 3.41-4.26 (br m, 5H); 6.61-6.67 (br m, 1H); 7.30-7.62 (m, 6H); 7.87-7.93 (br m, 1H); 8.58-8.64 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 484. Anal calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>: C, 62.09; H, 6.04; N, 8.69. Found: C, 61.96; H, 6.28; N, 8.49.

10

Example 209

(2-Isopropylphenyl)[2-nitro-4-( E-((3-isopropoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.07-1.21 (br m, 6H); 1.14 (d, J = 7.0 Hz, 6H); 2.52-3.16 (br m, 4H); 3.30-3.40 (m, 1H); 3.41-4.24 (br m, 3H); 4.81-4.97 (m, 1H); 6.61-6.68 (br m, 1H); 7.32-7.63 (m, 6H); 7.87-7.94 (br m, 1H); 8.60-8.66 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 498. Anal calcd for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>: C, 62.76; H, 6.28; N, 8.44. Found: C, 62.51; H, 6.52; N, 8.14.

20

Example 210

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(dimethylaminocarbonyl)-4-methylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 2.14 (s, 3H); 2.82, 2.84 (s, s, 3H); 3.12 (s, 3H); 2.12-4.24 (br m, 8H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.62 (m, 6H); 7.87-7.94 (br m, 1H); 8.60-8.66 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 497. Anal calcd for C<sub>26</sub>H<sub>32</sub>N<sub>4</sub>S<sub>1</sub>O<sub>4</sub>·0.42H<sub>2</sub>O: C, 61.94; H, 6.56; N, 11.11. Found: C, 62.00; H, 6.78; N, 10.89.

Example 211

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carbomethoxy-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 1.59-1.75 (br m, 2H); 2.50-3.14 (br m, 1H); 3.30-3.40 (m, 1H); 3.60, 3.61 (s, s, 3H); 4.01-4.44 (br m, 4H); 5.05-5.10 (br m, 1H); 6.63 (d, J = 8.5 Hz, 1H); 7.34-7.62 (m, 6H); 7.87-7.94 (br m, 1H); 8.60-8.66 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 485.

Example 212

(2-Isopropylphenyl)[2-nitro-4-( E-((3-hydroxymethyl-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.49-1.90 (br m, 2H); 2.75-3.14 (br m, 1H); 3.30-3.40 (m, 1H); 3.40-4.23 (br m, 5H); 4.38-4.52 (m, 1H); 4.60-4.73 (m, 1H); 6.61-6.66 (m, 1H); 7.27-7.61 (m, 6H); 7.84-7.93 (br m, 1H); 8.54-8.63 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 457. Anal calcd for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>S<sub>1</sub>O<sub>5</sub>·0.47H<sub>2</sub>O: C, 61.97; H, 6.27; N, 6.02. Found: C, 62.02; H, 6.49; N, 5.90.

### Example 213

(2-Ethoxyphenyl)[2-trifluoromethyl-4-( E-((2-carbomethoxy-4-(methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 71. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.80 (s, 1H), 7.66 (d, 1H, J = 15.4 Hz), 7.45 (dd, 1H, J = 1.6, 7.5 Hz), 7.48 (m, 2H), 7.01 (d, 1H, J = 6.6 Hz), 6.95 (d, 1H, J = 6.8 Hz), 6.90 (m, 2H), 5.34 (br s, 1H), 4.66 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.18 (m, 1H), 3.00 (m, 3H). MS (ESI) m/z 553, 575.

### Example 214

(2-Ethoxyphenyl)[2-trifluoromethyl-4-( E-((2-carbomethoxy-4-methyl piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 71. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.79 (s, 1H), 7.64 (d, 1H, J = 15.3 Hz), 7.45 (dd, 1H, J = 1.7, 7.8 Hz), 7.4-7.35 (m, 2H), 7.01 (d, 1H, J = 8.1 Hz), 6.97 (dd, 1H, J = 1.2, 7.6

Hz), 6.87-7.91 (m, 2H), 5.36 (br s, 1H), 3.98 (q, 2H,  $J = 6.9$  Hz), 3.90 (m, 1H), 3.78 (s, 3H), 3.65 (m, 1H), 3.42 (m, 1H), 2.85 (m, 1H), 2.32 (s, 3H), 2.24 (m, 1H), 2.19 (m, 1H), 1.18 (t, 3H,  $J = 6.9$  Hz). MS (ESI)  $m/z$  509, 531.

5

Example 215

(2-Ethoxyphenyl)[2-trifluoromethyl-4-(*E*-((2-carboxy-4-(methoxycarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 71.

<sup>1</sup>H NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  8.10 (m, 1H), 7.68 (m, 1H), 7.42 (m, 2H), 7.30 (m, 1H), 7.20 (d, 1H,  $J = 15.6$  Hz), 7.10 (d, 1H,  $J = 8.1$  Hz), 7.04 (d, 1H,  $J = 8.5$  Hz), 6.98 (d, 1H,  $J = 7.5$  Hz), 4.65 (br s, 1H), 4.53 (m, 2H), 4.05 (m, 2H), 4.00 (q, 2H,  $J = 6.9$  Hz), 3.57 (s, 3H), 1.09 (t, 3H,  $J = 6.9$  Hz). MS (ESI)  $m/z$  -537, -569.

15

Example 216

(Indol-6-yl)[2-chloro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 6-bromoindole, isolated as a white solid. <sup>1</sup>H NMR ( $d_6$ -DMSO, 300 MHz)  $\delta$  2.03 (s, 3H), 3.40-3.77 (m, 8H), 6.52-6.55 (m, 1H), 6.60 (d,  $J = 8.4$  Hz, 1H), 7.13 (dd,  $J = 1.8, 8.4$  Hz, 1H), 7.27 (d,  $J = 15.6$  Hz, 1H), 7.40 (d,  $J = 15.6$  Hz, 1H), 7.43 (dd,  $J = 1.8, 8.4$  Hz, 1H), 7.51 (t,  $J = 3.0$  Hz, 1H), 7.64 (m, 1H), 7.70 (d,  $J = 8.4$  Hz, 1H), 7.99 (d,  $J = 1.8$  Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  440, 442.

Example 217

(1-Ethyl,3-(dimethylaminomethyl)indol-7-yl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

- 5 The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 7-bromo-3-*N,N*-dimethylmethyl-*N*-ethyl indole, and isolated as a light-brown solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.30 (t, *J* = 7.05 Hz, 3H), 2.14 (s, 3H), 2.41 (s, 6H), 2.93-3.05 (m, 2H), 3.47-3.55 (m, 2H), 3.55-3.87 (m, 6H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 15.6 Hz, 1H), 7.09 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H), 7.81 (dd, *J* = 0.9, 7.8 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 525, 527.

Example 218

- 15 (5-Ethoxybenzodioxan-6-yl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 6-bromo-5-ethoxybenzodioxane, as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.14 (s, 3H), 3.54 (br s, 2H), 3.60-3.88 (m, 6H), 4.06 (q, *J* = 7.2 Hz, 2H), 4.33 (s, 4H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 15.6 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.17 (dd,

*Sub AS6*  
 $J = 1.8, 8.4 \text{ Hz, 1H), 7.50 (d, } J = 1.8 \text{ Hz, 1H), 7.57 (d, } J = 15.6 \text{ Hz, 1H). MS (APCI^+)$   
 $(M+H)^+$  at  $m/z$  503, 505.

Example 219

5     (2-Ethyl-4-bromophenyl)[2-nitro-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 32.

$^1\text{H NMR (CDCl}_3\text{, 300 MHz)} \delta$  8.43 (d, 1H,  $J = 2.0 \text{ Hz}$ ), 7.64 (d, 1H,  $J = 15.6 \text{ Hz}$ ), 7.58  
 (d, 1H,  $J = 2.0 \text{ Hz}$ ), 7.40-7.48 (m, 3H), 6.90 (d, 1H,  $J = 15.2 \text{ Hz}$ ), 6.90 (d, 1H,  $J = 8.5$   
 10     Hz), 3.63-3.77 (m, 6H), 3.54 (m, 2H), 2.72 (q, 2H,  $J = 7.5 \text{ Hz}$ ), 2.15 (s, 3H), 1.18 (t,  
 3H,  $J = 7.5 \text{ Hz}$ ). MS (ESI)  $m/z$  518, 520, 542, 627. Anal. Calcd for  $\text{C}_{23}\text{H}_{24}\text{Br}_1\text{N}_3\text{O}_4\text{S}$   
 : C, 53.08; H, 4.60; N, 7.93. Found: C, 53.29, H, 4.67, N, 8.11.

Example 220

15     (Benzodioxan-6-yl)[2-nitro-4-(*E*-((2-carboxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the hydrolysis of the compound of

Example 203 under basic conditions (aq. NaOH/EtOH), producing a light yellow  
 solid; mp  $165^\circ\text{C(dec.)}$ .  $^1\text{H NMR (DMSO-}d_6\text{, 300 MHz)} \delta$  1.15-1.52 (m, 3H), 1.46-  
 20     1.62 (m, 2H), 2.32 (m, 1H), 2.80 (m, 1H), 3.45(br, 1/2H), 4.00 (br, 1/2H), 4.44 (br,  
 1/2H), 4.800 (br, 1/2H), 6.83 (d,  $J=8.0 \text{ Hz}$ , 1H), 7.03 (d,  $J=8.0 \text{ Hz}$ , 1H), 7.09 (dd,  
 $J=2.0, 14.0 \text{ Hz}$ , 1H), 7.15 (d,  $J=2.0 \text{ Hz}$ , 1H), 7.20 (d,  $J=15.5 \text{ Hz}$ , 1H), 7.35 (d,  $J=15.5$

Hz, 1H), 7.73 (m, 1H), 8.52 (m, 1H). MS (ESI)  $m/z$  469 (M-H)<sup>+</sup>, 471 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>23</sub>H<sub>21</sub>N<sub>2</sub>O<sub>7</sub>SNa • NaOH • 2.7 H<sub>2</sub>O: C, 47.54; H, 4.75; N, 4.82. Found: C, 47.18; H, 4.36; N, 4.89.

5

Example 221

(Benzodioxan-6-yl)[2-nitro-4-(E-((4-carboxymethylpiperazin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

10 The title compound was prepared by deprotection of the compound 33 with  
TFA in CH<sub>2</sub>Cl<sub>2</sub>. The resultant free amine was treated with *tert*-butyl bromoacetate  
and TEA in acetonitrile at room temperature, and followed by deprotection with TFA  
in CH<sub>2</sub>Cl<sub>2</sub>, giving a light solid, mp 120 °C (dec.). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ  
3.20-3.45 (m, 4H), 4.20 (s, 2H), 3.50-3.80 (m, 4H), 4.28-4.46 (m, 4H), 6.86 (d, J=8.5  
Hz, 1H), 7.04 (m, J=8.0 Hz, 1H), 7.09 (dd, J=2.0 8.0 Hz, 1H), 7.15 (d, J=2.0 Hz, 1H),  
15 7.40 (d, J=15.5 Hz, 1H), 7.56 (d, J=15.0 Hz, 1H), 7.90 (dd, J=2.0, 8.5 Hz, 1H), 8.63  
(m, 1H). MS (ESI)  $m/z$  484 (M-H)<sup>+</sup>, 486 (M+H)<sup>+</sup>. Calcd. Anal for  
C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>7</sub>S • 1.19 CF<sub>3</sub>COOH • 1.34 H<sub>2</sub>O: 47.63; H, 4.11; N, 6.89. Found: C, 47.93; H,  
4.51; N, 6.49.

20

Example 222

(3-Morpholinophenyl)[2-nitro-4-(E-((4-acetylpiperazin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 62, employing the compound of Example 103 as starting material. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.80 (s, 1H), 7.64 (d, 1H, J = 15.4 Hz), 7.43 (m, 1H), 7.32 (t, 1H, J = 8.1 Hz), 7.08 (m, 2H), 6.99 (m, 2H), 6.84 (d, 1H, J = 15.4 Hz), 3.87 (t, 4H, J = 4.8 Hz), 3.63-3.79 (m, 6H), 3.50-3.55 (m, 2H), 3.18 (t, 4H, J = 4.8 Hz), 2.10 (s, 3H). MS (ESI) *m/z* 520, 542, 1061.

#### Example 223

(5-Ethoxybenzodioxan-8-yl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 8-bromo-5-ethoxybenzodioxane, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.52 (t, *J* = 7.2 Hz, 3H), 2.15 (s, 3H), 3.48-3.59 (m, 2H), 3.59-3.85 (m, 6H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.22-4.30 (m, 2H), 4.30-4.40 (m, 2H), 6.59 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.78 (d, *J* = 15.6 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 7.17 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.58 (d, *J* = 15.6 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 503, 505.

#### Example 224

(5-Chloro-8-ethoxyquinolin-7-yl)[2-chloro-4-( *E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 5-chloro-8-ethoxy-7-iodoquinoline, giving a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.37 (t, *J* = 7.2 Hz, 3H), 2.04 (s, 3H), 3.41-3.82 (m, 8H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.29 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 15.6 Hz, 1H), 7.51 (d, *J* = 15.6 Hz, 1H), 7.68 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.74 (dd, *J* = 3.9, 8.4 Hz, 1H), 8.15 (s, 1H), 8.55 (dd, *J* = 1.8, 8.4 Hz, 1H), 9.05 (dd, *J* = 1.8, 3.9 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 530, 532, 534.

#### Example 225

10     (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

#### Example 225A

(2-Isopropylphenyl)[2-nitro-4-(*E*-(carboxy)ethenyl)phenyl] sulfide

Sub  
Asp  
15     To a stirred mixture of 4-chloro-3-nitrocinnamic acid (500 mg, 2.2 mmol) in 5 mL of anhydrous DMF with K<sub>2</sub>CO<sub>3</sub> (911 mg, 6.6 mmol) was added 2-isopropylbenzenethiol (372 mL, 2.2 mmol) in 1 mL of DMF dropwise. The resulting mixture was then heated at 70 °C under nitrogen atmosphere over night. Water (25 mL) was then added and the reaction mixture was acidified to pH = 4 with 3N HCl.  
20     The cloudy mixture was extracted with EtOAc (2×20 mL). The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo to give the

Sub  
AS8

title compound as viscous light-yellow oil, which was used for coupling with further purification.

### Example 225B

5     (2-Isopropylphenyl)[2-nitro-4-( E-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl)  
          phenyl] sulfide

09541795-033100  
001100 " 56214500

The title compound was prepared by the procedures described in Example 92, substituting the benzoic acid with cinnamic acid from 225A, and ammonium chloride with ethyl nipecotate, giving a light-yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.18  
10   (d, *J* = 6.6 Hz, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.69-1.82 (m, 1H), 1.82-1.99 (m, 1H),  
1.99-2.20 (m, 1H), 2.45-2.62 (m, 2H), 3.45 (septet, *J* = 6.6 Hz, 1H), 3.56-3.80 (m,  
1H), 3.80-4.10 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.65-4.81 (m, 1H), 6.69 (d, *J* = 8.4  
Hz, 1H), 7.00 (br s, 1H), 7.31 (dd, *J* = 2.4, 6.9 Hz, 1H), 7.42 (br d, *J* = 8.4 Hz, 1H),  
7.51 (d, *J* = 15.6 Hz, 1H), 7.52 (overlapping d, 2H), 7.58 (d, *J* = 15.6 Hz, 1H), 8.43 (s,  
15   1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 483.

### Example 226

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)  
          phenyl] sulfide

20     The title compound was prepared by the procedures described in Example 155,  
substituting the ethyl ester from Example 137 with the ethyl ester from Example  
225B, and KOH with NaOH, to give a light-yellow solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300

MHz)  $\delta$  1.15 (d,  $J = 6.9$  Hz, 6H), 1.30-1.50 (m, 1H), 1.50-1.80 (m, 2H), 1.88-2.04 (m, 2H), 2.95-3.17 (m, 1H), 3.94-4.06 (m, 1H), 4.06-4.22 (m, 2H), 4.40-4.52 (m, 1H), 6.63 (d,  $J = 8.7$  Hz, 1H), 7.33-7.53 (m, 3H), 7.56-7.68 (m, 3H), 7.91 (dd,  $J = 1.8, 8.4$  Hz, 1H), 8.63 (d,  $J = 8.4$  Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  455.

5

Example 227

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((3-ethanesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

10 To a stirred solution of free acid (50 mg, 0.11 mmol) from Example 226 in 1 mL of methylene chloride was added ethyl sulfonamide (18 mg, 0.17 mmol), EDAC (25 mg, 0.13 mmol), and DAMP (2.7 mg, 0.022 mmol) sequentially. The mixture was stirred at ambient temperature for 16 h. The solvent was then removed on a rotavap under reduced pressure and the residue was purified on an Alltech sep-pak, eluting with 1% MeOH in EtOAc to give 30 mg (50 % yield) the title compound as a light

15 yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.18 (d,  $J = 6.3$  Hz, 6H), 1.34 (t,  $J = 7.5$  Hz, 3H), 1.61-1.74 (m, 2H), 1.84-2.04 (m, 1H), 2.13-2.35 (m, 1H), 2.60-2.75 (m, 2H), 3.44 (p,  $J = 7.5$  Hz, 2H), 3.53-3.66 (m, 1H), 3.66-3.85 (m, 2H), 4.00-4.18 (m, 1H), 6.71 (d,  $J = 8.7$  Hz, 1H), 6.88 (d,  $J = 15.6$  Hz, 1H), 7.31 (dd,  $J = 2.4, 8.4$  Hz, 1H), 7.41 (d,  $J = 1.8, 8.4$  Hz, 1H), 7.51 (d,  $J = 1.8$  Hz, 1H), 7.54 (d,  $J = 8.4$  Hz, 1H), 7.67 (d,  $J =$

20 15.6 Hz, 1H), 8.43 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  546.

Example 228

00547560 5674560

(2-Isopropylphenyl)[2-nitro-4-( E-(((3-(4-methylpiperazine)  
sulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 228, substituting ethyl sulfonamide with *N*-methylpiperazine sulfonamide, giving a light yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.18 (d, *J* = 6.5 Hz, 6H), 1.40-2.10 (m, 9H), 2.60 (s, 3H), 2.60-2.76 (m, 4H), 2.90 (br s, 3H), 3.44 (septet, *J* = 6.5 Hz, 1H), 3.52-4.08 (m, 4H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 15.6 Hz, 1H), 7.31 (d, *J* = 2.1, 8.4 Hz, 1H), 7.43-7.57 (m, 4H), 7.64 (d, *J* = 15.6 Hz, 1H), 8.44 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 616. Anal. Calcd for C<sub>29</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>S<sub>2</sub> · 1.13 H<sub>2</sub>O: C, 54.76; H, 6.22; N, 11.01. Found: C, 54.78; H, 6.11; N, 10.87.

Example 229

(2-Isopropylphenyl)[2-nitro-4-( E-(((3-*p*-toluenesulfonylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 228, substituting ethyl sulfonamide with *p*-toluenesulfonamide, giving a light yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.19 (d, *J* = 6.5 Hz, 6H), 1.75-1.94 (m, 2H), 2.05-2.24 (m, 1H), 2.40 (s, 3H), 2.48-2.60 (m, 2H), 3.45 (septet, *J* = 6.5 Hz, 1H), 3.50-3.85 (m, 3H), 3.85-4.12 (m, 1H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 15.6 Hz, 1H), 7.27-7.34 (m, 2H), 7.43 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.50 (overlapping d, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 8.44 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 608.

5 Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 0.94-1.18 (m, 3H); 1.14 (d, J = 7.0 Hz, 6H); 1.98-2.08 (br m, 3H); 2.69-3.74 (br m, 4H); 4.02-4.65 (br m, 4H); 6.64 (d, J = 8.5 Hz, 1H); 7.31-7.63 (m, 6H); 7.88-7.96 (br m, 1H); 8.65 (br s, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 468. Anal calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>4</sub>·0.1H<sub>2</sub>O: C, 63.91; H, 6.70; N, 8.94. Found: C, 63.54; H, 6.41; N, 8.67.

(2-Hydroxyphenyl)-[2-chloro-4-(*E*)-[(morpholin-1-yl)carbonyl]ethenyl]phenyl]sulfide

The title compound was prepared according to the procedures of Example 1, giving a white solid, m.p. 157-158C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.60-3.76 (m, 8H), 6.42 (s, 1H), 6.57 (d, J=9hz, 1H), 6.76 (d, J=15Hz, 1H), 6.99-7.04 (m, 1H), 7.10-7.20 (m, 2H), 7.42-7.55 (m, 4H). Anal. Calcd. for C<sub>19</sub>H<sub>18</sub>ClNO<sub>3</sub>S: C, 60.71; h, 4.83; N, 3.73. Found: C, 60.48; H, 5.05; N, 3.69.

(1-(Carboxymethyl)indol-5-yl)[2-chloro-4-( *E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl] phenyl] sulfide

Sub  
A61

To a stirred solution of indole compound from Example 85 (35 mg, 0.080 mmol) in 1 mL of anhydrous DMSO was added crushed KOH (18 mg, 0.32 mmol). After 45 min, *t*-butyl bromoacetate (23.5 mL, 0.16 mmol) was added. The resulting mixture was stirred at ambient temperature for 10 h. Water was then added and the reaction mixture was acidified with 3 N HCl to pH = 3. The title compound (25 mg, 63 %) was collected through filtration and dried in vacuum oven, giving a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 2.04 (s, 3H), 3.38-3.80 (m, 8H), 4.59 (s, 2H), 6.45 (d, *J* = 3.0 Hz, 1H), 6.52 (d, *J* = 8.7 Hz, 1H), 7.21 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.25 (d, *J* = 15.6 Hz, 1H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.40 (d, *J* = 3.0 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.97 (s, 1H). MS (ESI<sup>+</sup>) (M-H)<sup>+</sup> at *m/z* 496, 498.

### Example 233

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

15 The title compound was prepared by the procedures described in Example 84, substituting 2-bromothiophenol with 6-mercaptobenzenedioxane. white solid; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.15 (s, 3H), 3.46-3.89 (m, 8H), 4.30 (dd, *J* = 2.1, 6.0 Hz, 4H), 6.84 (d, *J* = 15.0 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.97-7.10 (m, 3H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 15.0 Hz, 1H), 7.77 (s, 1H). MS (ESI<sup>+</sup>) *m/z* 493 (M+H)<sup>+</sup>.

20

### Example 234

Sub  
A62

Sub  
A62

(2-Isopropylphenyl)[2-nitro-4-(E-((3-(1-pyrrolidin-2-onyl)prop-1-ylamino)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.1 Hz, 6H); 1.58-1.68 (m, 2H); 1.85-1.97 (m, 2H); 2.18-2.24 (m, 2H); 3.10-3.22 (m, 4H); 3.30-3.39 (m, 3H); 6.65-6.72 (m, 2H); 7.32-7.45 (m, 2H); 7.57-7.62 (m, 3H); 7.76 (dd, J = 8.8, 2.0 Hz, 1H); 8.11-8.17 (m, 1H); 8.44 (d, J = 2.0 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 468. Anal calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>S<sub>1</sub>O<sub>4</sub>·0.26CH<sub>3</sub>COOCH<sub>2</sub>CH<sub>3</sub>: C, 63.77; H, 6.39; N, 8.57. Found: C, 63.46; H, 6.37; N, 8.90.

Example 235

(3-(2-Morpholinoethylamino)phenyl)[2-trifluoromethyl-4-(E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 62, employing the compound of Example 103 as starting material. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.78 (d, 1H, J = 1.4 Hz), 7.64 (d, 1H, J = 15.4 Hz), 7.42 (d, 1H, J = 8.8 Hz), 7.21 (t, 1H, J = 7.9 Hz), 7.12 (d, 1H, J = 8.5 Hz), 6.84 (d, 1H, J = 15.4 Hz), 6.82 (m, 1H), 6.76 (t, 1H, J = 1.8 Hz), 6.66 (m, 1H), 3.72 (m, 10H), 3.51-3.55 (m, 2H), 3.16 (t, 2H, J = 5.9 Hz), 2.64 (t, 2H, J = 5.9 Hz), 2.50 (m, 4H), 2.15 (s, 3H). MS (ESI) m/z 563.

Example 236

(2-Pyrrolidin-1-ylphenyl)[2-nitro-4-(E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 62, employing the compound of Example 103 as starting material. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300  
5 MHz) δ 7.77 (s, 1H), 7.64 (d, 1H, J = 15.4 Hz), 7.40 (m, 1H), 7.22 (d, 1H, J = 7.8 Hz),  
7.10 (d, 1H, J = 8.8 Hz), 6.82 (d, 1H, J = 15.3 Hz), 6.76 (d, 1H, J = 7.8 Hz), 6.70 (t,  
1H, J = 2.0 Hz), 6.59 (dd, 1H, J = 2.4, 8.1 Hz), 3.61-3.79 (m, 6H), 3.51-3.54 (m, 2H),  
3.28 (m, 4H), 2.14 (s, 3H), 2.01 (m, 4H). MS (ESI) *m/z* 504.

Example 237

(3-Bromophenyl)[2-nitro-4-(E-((3-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.40 (d, 1H, J = 1.5 Hz), 7.75 (m, 1H), 7.45 (m, 1H),  
15 7.48-7.56 (m, 2H), 7.38 (t, 1H, J = 7.9 Hz), 7.00 (br, 1H), 6.87 (d, 1H, J = 9.5 Hz),  
4.16 (q, 2H, J = 7.1 Hz), 3.99 (br, 2H), 3.70 (br, 1H), 3.30 (br, 1H), 3.00 (br, 1H), 2.55  
(s, 1H), 2.10 (m, 1H), 1.89 (br, 1H), 1.85 (br, 1H), 1.27 (t, 3H, J = 7.0 Hz). MS (ESI)  
*m/z* 519, 521. Anal. Calcd for C<sub>23</sub>H<sub>23</sub>BrN<sub>2</sub>O<sub>5</sub>S · 0.19 H<sub>2</sub>O: C, 52.84; H, 4.51; N,  
5.36. Found: C, 52.85; H, 4.55; N, 5.28.

Example 238

(3-Bromophenyl)[2-nitro-4-(*E*-((4-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.41 (s, 1H), 7.75 (m, 1H), 7.62-7.67 (m, 2H), 7.53 (m,  
5 1H), 7.48 (d, 1H, *J* = 8.8 Hz), 7.38 (t, 1H, *J* = 7.9 Hz), 6.98 (br, 1H), 6.88 (d, 1H, *J* =  
8.5 Hz), 4.18 (q, 2H, *J* = 7.1 Hz), 3.64-78 (br, 4H), 3.55 (br, 4H), 1.29 (t, 3H, *J* = 7.0  
Hz). MS (ESI) *m/z* 520, 522.

Example 239

10 (2-(Hydroxymethyl)-benzodioxan-6-yl)[2-chloro-4-(*E*-((4-acetyl)piperazin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 85,  
substituting 5-iodoindole with a mixture of 2-hydroxymethyl-6-bromobenzodioxane  
and 2-hydroxymethyl-7-bromobenzodioxane, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>,  
15 300 MHz, mixture of 3:2 regioisomers) δ 2.15 (s, 3H), 3.46-3.83 (m, 8H), 3.83-4.01  
(m, 2H), 4.10-4.42 (m, 4H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 15.9 Hz, 1H), [6.95  
(d), 6.98 (d), *J* = 4.8 Hz, 1H in total], [7.04 (t), 7.07 (t), *J* = 1.5 Hz, 1H in total], [7.10  
(d), 7.11 (d), *J* = 2.4 Hz, 1H in total], 7.19 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 7.58 (d, *J*  
= 15.6 Hz, 1H). MS (APCI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 489.

Sub  
Ab 3

Sub  
A63

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 233, substituting 1-acetylpiperazine with 3-aminopropyl-1-pyrrolidin-2-one, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.69-1.80 (m, 2H), 2.08 (p, *J* = 7.5 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 3.27-3.48 (m, 6H), 4.24-4.34 (m, 4H), 6.44 (d, *J* = 15.6 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.01 (dd, *J* = 2.7, 8.4 Hz, 1H), 7.06 (d, *J* = 2.7 Hz, 1H), 7.08 (s, 1H), 7.40 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.53 (d, *J* = 15.6 Hz, 1H), 7.75 (d, *J* = 2.1 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 507.

#### Example 241

(3-(Dimethylaminomethyl)indol-5-yl)[2-chloro-4-(E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Sub  
A64

The title compound was prepared by the procedures described in Example 217, substituting the indole from 186 with the indole from Example 85, resulting in a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.15 (s, 3H), 2.54 (s, 6H), 3.47-3.85 (m, 8H), 4.05 (s, 2H), 6.56 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 15.6 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.52 (s, 2H), 7.56 (d, *J* = 15.6 Hz, 1H), 7.88 (s, 1H), 9.27 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 497, 499. Anal. Calcd for C<sub>26</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>2</sub>S · 0.46 TFA · 1.72 MeOH: C, 56.89; H, 6.06; N, 9.27. Found: C, 56.83; H, 6.15; N, 9.46.

Example 242

(2-Isopropylphenyl)[2-nitro-4-( E-((2-carboethoxypiperidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the procedures described in Example 225,  
5 substituting ethyl nipecotate with ethyl pipecolate, giving a light-yellow solid. <sup>1</sup>H  
NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.18 (d, *J* = 6.9 Hz, 6H), 1.28 (t, *J* = 7.35 Hz, 3H), 1.34-  
1.62 (m, 2H), 1.62-1.84 (m, 3H), 2.32 (br d, *J* = 13.2 Hz, 1H), 3.33-3.54 (m, 1H), 3.45  
(septet, *J* = 6.9 Hz, 1H), 3.99 (br d, *J* = 13.2 Hz, 1H), 4.21 (q, *J* = 7.35 Hz, 2H), 5.46  
(br s, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 15.6 Hz, 1H), 7.25-7.34 (m, 1H), 7.42  
10 (d, *J* = 8.7 Hz, 1H), 7.46-7.60 (m, 3H), 7.58 (d, *J* = 15.6 Hz, 1H), 8.44 (s, 1H). MS  
(ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 483.

Example 243

(2-Isopropylphenyl)[2-nitro-4-( E-((2-carboxypiperidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the procedures described in Example 226,  
substituting the ethyl ester from Example 225 with the ethyl ester from Example 242,  
giving a light-yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.18 (d, *J* = 6.9 Hz, 6H),  
1.40-1.89 (m, 5H), 2.34 (br d, *J* = 11.7 Hz, 1H), 3.31-3.51 (m, 1H), 3.44 (septet, *J* =  
15 6.9 Hz, 1H), 4.01 (d, *J* = 11.7 Hz, 1H), 5.42 (br s, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.99  
(br d, *J* = 15.6 Hz, 1H), 7.29 (td, *J* = 2.7, 6.9 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.45-  
20 7.58 (m, 3H), 7.64 (d, *J* = 15.6 Hz, 1H), 8.43 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 455.



3.20-3.42 (m, 1H), 3.44 (septet,  $J = 6.9$  Hz, 1H), 3.97-4.18 (m, 1H), 4.40-4.65 (m, 1H), 6.70 (d,  $J = 8.7$  Hz, 1H), 6.97 (d,  $J = 15.6$  Hz, 1H), 7.30 (td,  $J = 2.7, 6.9$  Hz, 1H), 7.41 (d,  $J = 8.7$  Hz, 1H), 7.46-7.65 (m, 3H), 7.60 (d,  $J = 15.6$  Hz, 1H), 8.43 (s, 1H).  
MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  455.

5

Example 246

(2-Isopropylphenyl)[2-nitro-4-(*E*-(((4-*p*-toluenesulfonylamino  
carbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

10 The title compound was prepared by the procedures described in Example 229,  
substituting the acid from Example 226 with the acid from Example 245. light-yellow  
solid; <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz)  $\delta$  1.14 (d,  $J = 6.9$  Hz, 6H), 1.18-1.39 (m, 2H),  
1.67-1.79 (m, 2H), 2.39 (s, 3H), 2.60-2.75 (m, 1H), 2.96-3.14 (m, 1H), 3.26-3.42 (m,  
1H), 3.34 (septet,  $J = 6.9$  Hz, 1H), 4.10-4.42 (m, 2H), 6.62 (d,  $J = 8.4$  Hz, 1H), 7.32-  
7.43 (m, 4H), 7.45 (d,  $J = 15.6$  Hz, 1H), 7.58 (d,  $J = 8.4$  Hz, 2H), 7.60 (d,  $J = 3.6$  Hz,  
15 1H), 7.78 (d,  $J = 8.4$  Hz, 2H), 7.87 (dd,  $J = 2.7, 8.4$  Hz, 1H), 8.60 (d,  $J = 2.7$  Hz, 1H).  
MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  606. Anal. Calcd for C<sub>31</sub>H<sub>33</sub>N<sub>3</sub>O<sub>6</sub>S<sub>2</sub> · 0.26 H<sub>2</sub>O: C,  
60.80; H, 5.52; N, 6.86. Found: C, 60.85; H, 5.84; N, 6.61.

Example 247

20 (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxy-4-hydroxypiperidin-1-  
yl)carbonyl)ethenyl) phenyl] sulfide

- Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.53-1.70 (br m, 2H); 2.92-3.52 (br m, 1H); 3.30-3.40 (m, 1H); 3.98-4.44 (br m, 4H); 4.90-5.20 (br m, 1H); 6.63 (d, J = 8.5 Hz, 1H); 7.34-7.62 (m, 6H); 7.87-7.94 (br m, 1H); 8.58-8.64 (br m, 1H).
- 5 MS (APCI) (M+H)<sup>+</sup> at m/z 471. Anal calcd for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>S<sub>1</sub>O<sub>6</sub>: C, 61.26; H, 5.57; N, 5.95. Found: C, 61.05; H, 5.85; N, 5.73.

#### Example 248

10 (Benzodioxan-6-yl)[2-trifluoromethyl-4-( E-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

- The title compound was prepared by the procedures described in Example 240 substituting N-(3'-aminopropyl)-2-pyrrolidinone with ethyl nipecotate, giving a white hygroscopic solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.26 (t, J=7.0 Hz, 3H), 1.54 (m, 1H), 1.65-1.80 (m, 2H), 2.10 (m, 1H), 2.54 (m, 1H), 2.92-3.40 (m, 2H), 3.60-4.10 (m, 15 2H), 4.14 (q, J=7.0 Hz, 2H), 4.25-4.32 (m, 4H), 6.91 (d, J=7.5 Hz, 1H), 7.00 (dd, J=2.0, 15.0 Hz, 3H), 7.05 (d, J=2.0 Hz, 1H), 7.40 (d, J=8.0, 1H), 7.56 (d, J=15.0 Hz, 1H), 7.76 (s, 1H). MS (CI/NH<sub>3</sub>) m/z 522 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>26</sub> H<sub>26</sub>F<sub>3</sub>NO<sub>5</sub>S: C, 59.88; H, 5.02; N, 2.69. Found: C; 59.92; H, 5.39; N, 2.56.

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#### Example 249

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( E-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 240 substituting N-(3'-aminopropyl)-2-pyrrolidinone with ethyl pipercolinate. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.28 (t, J=7.0 Hz, 3H), 1.35-1.54 (m, 2H), 1.64-1.82 (m, 3H), 2.30 (m, 1H), 3.40 (m, 1H), 4.00 (m, 1H), 4.22 (q, J=7.0 Hz, 2H), 4.26-4.34 (m, 4H), 5.48 (m, 1H), 6.91 (d, J=8.5 Hz, 1H), 6.98 (m, 1H), 7.02 (dd, J=2.0, 8.0 Hz, 2H), 7.06 (d, J=2.0 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.57 (d, J=15.0 Hz, 1H), 7.77 (s, 1H). MS (CI/NH<sub>3</sub>) m/z 522 (M+H)<sup>+</sup>. Anal. calcd for C<sub>26</sub>H<sub>26</sub>F<sub>3</sub>NO<sub>5</sub>S: C, 59.88; H, 5.02; N, 2.69. Found: C, 60.25; H, 5.12; N, 2.55.

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Example 250

(Benzodioxan-6-yl)[2-nitro-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the hydrolysis of compound 198 under basic condition (aq. NaOH/EtOH), and purified by reversed-phase HPLC. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.44 (m, 2H), 1.78 (m, 2H), 2.04 (m, 2H), 2.82 (m, 1H), 4.02-4.20 (m, 2H), 4.4.20-4.35 (m, 4H), 6.90 (d, J=8.0 Hz, 1H), 6.97 (d, J=8.0 Hz, 1H), 7.05 (dd, J=2.0, 8.0 Hz, 1H), 7.10 (d, J=2.0 Hz, 1H), 7.15 (br, 1H), 7.44 (m, 1H), 7.60 (br, 1H), 8.40 (s, 1H). MS (ESI) m/z 469 (M-1)<sup>-</sup>.

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Example 251

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carboxypyrrolidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of

Example 1. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.75 (s, 1H), 7.60 (d, 1H, J = 15.0 Hz) 7.40 (br, 1H), 7.06 (d, 1H, J = 2.2 Hz), 6.96-7.02 (m, 3H), 6.90 (d, 1H, J = 8.5 Hz), 4.30 (m, 5H), 3.99 (br, 2H), 3.29 (br, 2H), 2.60 (br, 2H), 1.85 (br, 2H). MS (ESI) *m/z* -492.

#### Example 252

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( E-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 240 substituting N-(3'-aminopropyl)-2-pyrrolidinone with ethyl isonipecotate, giving a white sticky solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.26 (t, J=7.0 Hz, 3H), 1.68-1.80 (m, 2H), 1.98-2.10 (, 2H), 2.54-2.70 (m, 2H), 3.00-3.30 (br, 2H), 4.15 (m, 3H), 4.26-4.34 (m, 4H), 6.90 (d, J=8.0 Hz, 2H), 7.00 (dd, J=2.0, 8.0 Hz, 2H), 7.06 (d, J=2.0 Hz, 1H), 7.41 (m, 1H), 7.50 (br, 1H), 7.75 (s, 1H). MS (CI/NH<sub>3</sub>) *m/z* 522 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>24</sub>H<sub>22</sub>F<sub>3</sub>NO<sub>5</sub>S•0.1 H<sub>2</sub>O: C, 58.20; H, 4.52; N, 2.83. Found: C, 58.14; H, 4.69; N, 2.76.

#### Example 253

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( E-((2-carbomethoxy-4-tert-butoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 240 substituting N-(3'-aminopropyl)-2-pyrrolidinone with 1-Boc-3-carbomethoxypiperazine, giving a white solid, mp 85-87 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.46 (s, 9H), 2.90-3.00 (m, 2H), 3.08-3.20 (m, 2H), 3.76 (s, 3H), 3.90 (m, 1H), 4.25-4.34 (m, 4H), 4.58-4.66 (m, 2H), 6.92 (d, J=8.0 Hz, 1H), 6.98 (m, 1H), 7.02 (dd, J=2.0, 8.0 Hz, 2H), 7.06 (d, J=2.0 Hz, 1H), 7.40 (m, 1H), 7.62 (br, 1H), 7.76 (s, 1H). MS (APCI) m/z 609 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>29</sub>H<sub>31</sub>F<sub>3</sub>N<sub>2</sub>O<sub>7</sub>S: C, 57.23; H, 5.13; N, 4.60. Found: C, 57.09; H, 5.25; N, 4.37.

#### Example 254

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carbomethoxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by treating the compound of Example 255 with methyl chloroformate and pyridine in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, producing a white foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.00 (m, 1H), 3.18 (m, 1H), 3.60 (m, 1H), 3.72 (s, 3H), 3.76 (s, 3H), 3.90 (m, 1H), 4.10 (br, 1H), 4.28-4.34 (m, 4H), 4.64 (m, 1H), 5.32 (m, 1H), 6.85 (d, J=15.5 Hz, 1H), 6.92 (d, J= 8.0 Hz, 1H), 6.98 (m, 1H), 7.02 (dd, J=2.0, 8.0 Hz, 1H), 7.08 (d, J=2.0 Hz, 1H), 7.40 (d, J=8.0 Hz, 1H), 7.64 (d, J=15.0 Hz, 1H), 7.77 (s, 1H). MS (CI/NH<sub>3</sub>) m/z 567 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>26</sub>H<sub>25</sub>F<sub>3</sub>N<sub>2</sub>O<sub>7</sub>S: C, 55.12; H, 4.45; N, 4.94. Found: C, 55.18; H, 4.70; N, 4.68.

#### Example 255

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( E-((2-carbomethoxypiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by deprotection of compound 253 with TFA in CH<sub>2</sub>Cl<sub>2</sub>, resulting in a light yellow solid, mp 70-72 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.90 (m, 1H), 3.05 (m, 1H), 3.35 (m, 1H), 3.68 (m, 1H), 3.80 (s, 3H), 4.00 (m, 1H), 4.25-4.34 (m, 4H), 4.70 (br, 1H), 5.46 (m, 1H), 6.84 (d, J=15.5 Hz, 1H), 6.90 (d, J=8.0 Hz, 1H), 6.96-7.04 (m, 2H), 7.06 (m, 1H), 7.40 (d, J=8.0 Hz, 1H), 7.65 (d, J=15.5 Hz, 1H), 7.77 (s, 1H). MS (CI/NH<sub>3</sub>) m/z 509 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>24</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>S•1.55 H<sub>2</sub>O: C, 53.74; H, 4.90; N, 5.22. Found: C, 54.04; H, 4.59; N, 4.82.

Example 256

(2-Methyl-3-(carboethoxymethyl)indol-5-yl)[2-trifluoromethyl-4-( E-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Example 256A

(4-Bromophenyl)[2-trifluoromethyl-4-( E-((morpholin-1-yl)carbonyl) ethenyl) phenyl] sulfide

The bromide was prepared by the procedure described in Example 12, substituting 2-bromothiophenol with 4-bromothiophenol, and 3,4-dichlorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde.

Example 256B

(4-Hydrazinophenyl)[2-trifluoromethyl-4-( E-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide, benzophenone hydrazone

To a stirred solution of above-described bromide (1.0 g, 2.12 mmol) in 10 mL  
5 of toluene with Pd(OAc)<sub>2</sub> (9.5 mg, 0.04 mmol), BINAP (40 mg, 0.06 mmol), and  
benzophenone hydrazone (437 mg, 2.12 mmol) was added NaOt-Bu (285 mg, 2.97  
mmol). The reaction mixture was bubbled with N<sub>2</sub> for 2 min before it was heated at 80  
°C for 4 h. The reaction mixture was then allowed to cool down to ambient  
temperature. Ether was then added and the mixture was filtered through celite, washed  
10 with diethyl ether. The filtrate was concentrate in vacuo and the residue was purified  
on a SiO<sub>2</sub> flash column chromatography eluting with 10-30% EtOAc/hexanes to give  
170 mg (13%) of the title compound as light brown foamy solid.

Example 256C

15 (2-Methyl-3-(carboethoxymethyl)indol-5-yl)[2-trifluoromethyl-4-( E-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

To a stirred solution of hydrazone (90 mg, 0.15 mmol) in 2 mL of ethanol was  
added levunilic acid (24 mL, 23 mmol) and *p*-TsOH (146 mg, 0.75 mmol). The  
mixture was then refluxed for 2 days. After cooled down to ambient temperature, the  
20 reaction mixture was partitioned between EtOAc and sat. NaHCO<sub>3</sub>. The organic layer  
was then washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The residue  
was then purified on Gilson preparative HPLC as described in Example 38B to give

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6.0 mg (7%) of the title compound. light-brown solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.20 (t,  $J = 7.4$  Hz, 3H), 2.46 (s, 3H), 3.55-3.83 (br m, 8H), 3.67 (s, 2H), 4.12 (q,  $J = 7.4$  Hz, 2H), 6.79 (d,  $J = 15.3$  Hz, 1H), 6.84 (d,  $J = 8.4$  Hz, 1H), 7.23-7.31 (m, 2H), 7.34 (d,  $J = 8.4$  Hz, 1H), 7.60 (d,  $J = 15.3$  Hz, 1H), 7.76 (s, 1H), 7.80 (s, 1H), 8.04 (s, 1H). MS (ESI $^+$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  533.

Example 257

(1-(2-Methoxyethyl)indol-5-yl)[2-chloro-4-(*E*-((4-acetyl)piperazin-1-yl)carbonyl)ethenyl] phenyl] sulfide

10 The title compound was prepared by the procedures described in Example 232, substituting *t*-butyl bromoacetate with bromoethylmethyl ether. white solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.14 (s, 2H), 3.35 (s, 3H), 3.46-3.56 (m, 2H), 3.56-3.80 (m, 6H), 3.75 (t,  $J = 5.6$  Hz, 2H), 4.33 (t,  $J = 5.6$  Hz, 2H), 6.54 (d,  $J = 3.3$  Hz, 1H), 6.61 (d,  $J = 8.7$  Hz, 1H), 6.75 (d,  $J = 15.3$  Hz, 1H), 7.09 (dd,  $J = 2.1, 11.7$  Hz, 1H), 7.26

15 (overlapping d, 1H), 7.36 (dd,  $J = 2.1, 8.7$  Hz, 1H), 7.44 (d,  $J = 8.7$  Hz, 1H), 7.51 (d,  $J = 2.1$  Hz, 1H), 7.56 (d,  $J = 15.3$  Hz, 1H), 7.88 (d,  $J = 1.5$  Hz, 1H). MS (ESI $^+$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  498, 500.

Example 258

20 (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-acetoxymethyl-4-hydroxypiperidin-1-yl)carbonyl)ethenyl] phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 1.51-1.90 (br m, 2H); 1.92-2.06 (m, 3H); 2.50-3.21 (br m, 2H); 3.30-3.40 (m, 1H); 3.40-4.44 (br m, 5H); 4.88-4.97 (br m, 1H); 6.63 (d, J = 8.5 Hz, 1H); 7.31-7.62 (m, 6H); 7.87-7.94 (br m, 1H); 8.58-8.64 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 499. Anal calcd for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>S<sub>1</sub>O<sub>6</sub>·0.29H<sub>2</sub>O: C, 61.98; H, 6.12; N, 5.56. Found: C, 62.00; H, 6.35; N, 5.55.

#### Example 259

10 (2-Isopropylphenyl)[2-nitro-4-( E-((3-(dimethylaminocarbonyl)-4-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.54-1.75 (br m, 2H); 2.81, 2.82 (br s, br s, 3H); 3.00, 3.04 (br s, br s, 3H); 2.75-3.60 (br m, 3H); 3.30-3.40 (m, 1H); 3.90-4.28 (br m, 2H); 4.95-5.28 (br m, 1H); 6.61-6.66 (m, 1H); 7.34-7.62 (m, 6H); 7.87-7.94 (br m, 1H); 8.58-8.63 (br m, 1H). MS (ESI) (M+H)<sup>+</sup> at m/z 498. Anal calcd for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>S<sub>1</sub>O<sub>5</sub>·0.34H<sub>2</sub>O: C, 61.99; H, 6.34; N, 8.34. Found: C, 61.96; H, 6.37; N, 8.56.

#### Example 260

20 (2-Isopropylphenyl)[2-nitro-4-( E-((3-cyanomorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 3.30-3.40 (m, 1H); 3.30-4.16 (br m, 5H); 4.20-4.29 (br m, 1H); 5.07 (t, J = 3.5 Hz, 1H); 6.65(d, J = 8.8 Hz, 1H); 7.32-7.44 (m, 2H); 7.54-7.62 (m, 4H); 7.91 (dd, J = 8.8, 2.0 Hz, 1H); 8.67 (d, J = 2.0 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 438. Anal calcd for C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>S<sub>1</sub>O<sub>4</sub>·0.25C<sub>6</sub>H<sub>14</sub>: C, 64.11; H, 5.82; N, 9.15. Found: C, 63.99; H, 6.00; N, 9.12.

#### Example 261

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carboethoxymorpholin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 1.12-1.27 (m, 3H); 3.30-3.40 (m, 1H); 3.15-4.33 (br m, 9H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.42 (m, 2H); 7.50-7.62 (m, 4H); 7.88-7.96 (br m, 1H); 8.65 (br s, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 485. Anal calcd for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>S<sub>1</sub>O<sub>6</sub>: C, 61.97; H, 5.82; N, 5.78. Found: C, 61.83; H, 6.07; N, 5.74.

#### Example 262

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The compound of Example 260 (160 mg, 0.336), sodium azide (56.6 mg, 0.872 mmol), n-Bu<sub>3</sub>SnCl and THF were mixed in a reaction tube, flushed with

nitrogen and heated to reflux overnight. The mixture was then cooled to ambient temperature and 1N HCl soln. was added. The mixture was extracted with ethyl acetate three times and the combined organics were dried over MgSO<sub>4</sub>. The mixture was filtered through a short silica gel plug to give 96 mg (56% yield) of the desired material. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 2.96-4.62 (br m, 7H); 4.77 (dd, J = 10.5, 2.7 Hz, 1H); 6.58-6.67 (m, 1H); 7.32-7.62 (m, 6H); 7.92 (dd, J = 8.8, 2.0 Hz, 1H); 8.62-8.67 (br m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 481. Anal calcd for C<sub>23</sub>H<sub>24</sub>N<sub>6</sub>S<sub>1</sub>O<sub>4</sub>·1.2H<sub>2</sub>O: C, 54.93; H, 5.31; N, 16.71. Found: C, 54.97; H, 5.12; N, 16.50.

#### Example 263

(Benzodioxan-6-yl)[2-trifluoromethyl-4-( E-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by hydrolysis of the compound of Example 252 under basic conditions (aq. NaOH/EtOH), giving a white solid, mp 88 °C (dec.). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.40 (m, 2H), 1.98 (m, 2H), 2.95 (m, 1H), 3.15 (m, 1H), 3.45 (m, 1H), 4.20 (m, 2H), 4.35 (m, 4H), 7.00 (m, 4H), 7.20 (m, 2H), 7.90 (m, 1H), 8.20 (m, 1H), 12.30 (s, 1H). MS (APCI) m/z 494 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>24</sub>H<sub>22</sub>F<sub>3</sub>NO<sub>3</sub>S·0.1 H<sub>2</sub>O: C, 58.20; H, 4.52; N, 2.83. Found: C, 58.14; H, 4.69; N, 2.76.

#### Example 264

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((2-carboxypiperidin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by hydrolysis of the compound of Example 249 under basic conditions (aq. NaOH/EtOH), resulting in a white solid, mp 90 °C

5 (dec.). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.15-1.50 (m, 2H), 1.50-1.70 (m, 2H), 2.16 (m, 1H), 2.56 (m, 1H), 3.15 (m, 1H), 4.30 (s, 4H), 4.32 (m, 1H), 5.20 (m, 1H), 7.02 (m, 4H), 7.30-7.52 (m, 2H), 7.84 (m, 1H), 8.15 (s, 1H). MS (APCI) *m/z* 494 (M+H)<sup>+</sup>.  
Anal. calcd. for C<sub>24</sub>H<sub>22</sub>F<sub>3</sub>NO<sub>5</sub>•0.3 H<sub>2</sub>O: C, 57.78; H, 4.57; N, 2.81. Found: C, 57.87;  
H, 4.5  
10 7; N, 2.76.

Example 265

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-carbomethoxypiperazin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide

15 The title compound was prepared according to the procedures of Example 1.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.76 (s, 1H), 7.62 (d, 1H, *J* = 15.0 Hz), 7.40 (d, 1H, *J* = 8.6 Hz) 7.06 (d, 1H, *J* = 2.1 Hz), 6.98-7.04 (m, 2H), 6.91 (d, 1H, *J* = 8.4 Hz), 6.84 (d, 1H, *J* = 15.6 Hz), 4.31 (m, 4H), 4.18 (q, 2H, *J* = 7.1 Hz), 3.68 (br, 4H), 3.54 (br s, 4H), 1.29 (t, 3H, *J* = 7.2 Hz). MS (ESI) *m/z* 523, 545, 1045, 1067.

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(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.13 (s, 1H), 7.84 (d, 1H, J = 9.0 Hz), 7.48 (d, 1H, J = 15.4 Hz) 7.38 (d, 1H, J = 15.4 Hz), 6.98-7.06 (m, 4H), 4.30 (m, 4H), 3.92 (s, 4H), 3.74 (br, 2H), 2.62 (br, 2H), 1.63 (br, 4H). MS (ESI) *m/z* 508, 1015.

#### Example 267

(Benzodioxan-6-yl)[2-trifluoro-4-(E-((4-(benzimidazol-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.32 (s, 1H), 7.79 (s, 1H), 7.66 (d, 1H, J = 15.4 Hz), 7.44 (d, 1H, J = 8.5 Hz), 7.0-7.12 (m, 6H), 6.94 (d, 1H, J = 9.9 Hz), 6.90 (d, 1H, J = 2.6 Hz), 4.98 (m, 1H), 4.59 (m, 1H), 4.20 (m, 5H), 3.31 (br, 1H), 2.83 (br, 1H), 2.40 (m, 2H), 1.98 (m, 2H). MS (ESI) *m/z* 582, 604, 1163, 1185.

#### Example 268

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((4-(methylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.75 (s, 1H), 7.67 (d, 1H, J = 15.4 Hz) 7.40 (d, 1H, J = 8.1 Hz), 7.06 (d, 1H, J = 2.4 Hz), 6.96-7.02 (m, 2H), 6.90 (d, 1H, J = 8.2 Hz), 4.28

(m, 4H), 3.95 (br, 2H), 3.50 (m, 1H), 2.82 (s, 3H), 2.40 (m, 1H), 2.15 (br, 1H), 1.88 (br, 1H), 1.73 (br, 2H). MS (ESI)  $m/z$  507, 529, 1035.

### Example 269

5        (Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-carbomethoxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 240 substituting N-(3'-aminopropyl)-2-pyrrolidinone with 2-carbomethoxy-1-methoxycarbonylpiperazine, producing a light yellow solid, mp 56 °C (dec.). <sup>1</sup>H  
10        NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.70-3.50 (br, 4H), 3.70 (s, 3H), 3.76 (d, J=9.0 Hz, 3H), 4.00(m, 1H), 4.20 (m, 4H), 4.50-5.00 (br, 2H), 6.91 (d, J=8.5 Hz, 1H), 6.92-7.02 (m, 2H), 7.07 (d, J=2.0 Hz, 1H), 7.25 (m, 1H), 7.40 (m, 1H), 7.60 (m, 1H), 7.72 (s, 1H). MS (APCI)  $m/z$  567 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>26</sub>H<sub>25</sub>F<sub>3</sub>N<sub>2</sub>O<sub>7</sub>S: C, 55.12; H, 4.45; N, 4.94. Found: C, 55.33; H, 4.74; N, 4.76.

### Example 270

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-carboxymorpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H  
20        NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 3.08-4.33 (br m, 7H); 3.30-3.40 (m, 1H); 6.58-6.68 (m, 1H); 7.32-7.66 (m, 6H); 7.87-7.94 (m, 1H); 8.53-8.65

(m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 457. Anal calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>S<sub>1</sub>O<sub>6</sub>: C, 60.51; H, 5.30; N, 6.14. Found: C, 60.33; H, 5.54; N, 5.80.

### Example 271

5                    (Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((2-carboxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

                  The title compound was prepared by treating the compound of Example 255 with methyl chloroformate and pyridine in CH<sub>2</sub>Cl<sub>2</sub> at room temperature, and followed by hydrolysis under basic conditions (aq. NaOH/EtOH), producing a white solid, mp  
10    102 °C (dec.). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.85 (m, 1H), 3.02 (m, 1H), 3.20 (m, 1H), 3.40 (m, 1H), 3.62 (s, 3H), 3.88 (m, 1H), 4.29 (s, 4H), 4.35 (m, 1H), 5.15 (m, 1H), 6.90-7.10 (m, 3H), 7.30 (d, J=15.0 Hz, 1 H), 7.40 (d, J=15.0 Hz, 1H), 7.54 (d, J=15.0 Hz, 1H), 7.82 (m, 1H), 8.15 (m, 1H). MS (ESI) m/z 553 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>7</sub>S• 0.25 H<sub>2</sub>O: C, 53.91; H, 4.25; N, 5.03. Found: 53.91; H, 4.35; N,  
15    5.05.

### Example 272

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20                    The title compound was prepared according to the procedures of Example 1. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.76 (s, 1H), 7.62 (d, 1H, J = 15.6 Hz), 7.40 (dd, 1H, J = 1.8, 8.2 Hz), 7.04 (d, 1H, J = 2.1 Hz), 6.98-7.03 (m, 2H), 6.91 (d, 1H, J = 8.1 Hz),

6.81 (d, 1H, J = 15.3 Hz), 4.30 (m, 4H), 3.65-3.74 (br m, 8H). MS (ESI)  $m/z$  452, 474, 925.

### Example 273

5     (Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.75 (s, 1H), 7.65 (d, 1H, J = 15.3 Hz), 7.40 (dd, 1H, J = 1.4, 8.3 Hz), 7.06 (d, 1H, J = 2.4 Hz), 6.98-7.02 (m, 2H), 6.90 (d, 1H, J = 8.1 Hz),  
10   6.85 (d, 1H, J = 15.3 Hz), 4.68 (m, 1H), 4.20 (m, 4H), 3.10 (m, 1H), 3.14 (m, 1H), 2.81 (s, 4H), 2.58 (br, 1H), 2.02 (s, 4H), 1.88 (s, 4H), 1.64 (m, 1H). MS (ESI)  $m/z$  519, 1037.

### Example 274

15   Sub  
    A68   (2-Isopropylphenyl)[2-nitro-4-(*E*-((3-aza-6,9-dioxaspiro[5.4]decan-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.44 (s, 1H), 7.50-7.62 (m, 4H), 7.41 (d, 1H, J = 8.0 Hz), 7.30 (m, 1H), 6.96 (br d, 1H, J = 15.6 Hz), 6.69 (d, 1H, J = 9.4 Hz), 4.00 (s, 4H),  
20   3.75 (br m, 4H), 3.44 (m, 1H), 1.75 (br s, 4H), 1.18 (d, 6H, J = 7.0 Hz). MS (ESI)  $m/z$  439, 937.

Example 275

(2-Isopropylphenyl)[2-nitro-4-(E-((2-(dimethylaminomethyl)piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

5 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.40 (d, 1H, J = 1.8 Hz), 7.50-7.58 (m, 4H), 7.42 (d, 1H, J = 8.1 Hz), 7.30 (dd, 1H, J = 1.9, 7.0 Hz), 7.00 (d, 1H, J = 15.4 Hz), 6.68 (d, 1H, J = 8.5 Hz), 5.10 (br, 1H), 3.92 (br, 1H), 3.44 (quintet, 1H, J = 6.9 Hz), 3.20 (m, 1H), 2.26-2.50 (m, 7H), 1.62-1.85 (m, 7H), 1.48 (m, 1H), 1.18 (d, 6H, J = 7.0 Hz). MS (ESI) *m/z* 468.

10

Example 276

(2-Isopropylphenyl)[2-nitro-4-(E-((piperidin-1-ylamino)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.44 (d, 1H, J = 1.8 Hz), 7.66 (d, 1H, J = 16.2 Hz), 7.55 (d, 1H, J = 7.4 Hz), 7.47-7.51 (m, 3H), 7.30 (m, 2H), 6.72 (d, 1H, J = 8.5 Hz), 6.37 (s, 1H), 3.48 (m, 2H), 3.10 (m, 2H), 2.63 (m, 1H), 1.81-1.89 (m, 2H), 1.62-1.77 (m, 4H), 1.19 (d, 6H, J = 7.0 Hz). MS (ESI) *m/z* 426, 851.

20

Example 277

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-carboxy-4-methoxycarbonylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by hydrolysis of the compound of Example 269 under basic conditions (aq. NaOH/EtOH). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 2.60-3.30 (m, 3H), 3.40-3.50 (m, 1H), 3.62 (d, J=12.0 Hz, 1H), 3.80 (m, 1H), 4.25-4.35 (m, 4H), 4.55 (m, 1H), 7.00 (s, 2H), 7.00-7.06 (m, 1H), 7.25 (m, 2H), 7.5 (m, 1H), 7.80 (m, 1H), 8.10 (m, 1H). MS (APCI) m/z 553 (M+H)<sup>+</sup>. Calcd. Anal. C<sub>24</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>5</sub>•1.55 H<sub>2</sub>O: C, 54.35; H, 4.20; N, 5.07. Found: C, 54.16; H, 4.19; N, 4.96.

#### Example 278

10 (2-(Dimethylaminocarbonyl)-benzodioxan-6-yl)[2-chloro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 85, substituting 5-iodoindole with 2-*N,N*-dimethylcarboxamide-6-bromobenzenedioxane and 3-*N,N*-dimethylcarboxamide-6-bromobenzenedioxane, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, mixture of regioisomers) δ 1.93 (s, 3H), 2.15 (s, 6H), 3.53 (br s, 2H), 3.59-3.90 (br m, 8H), 4.86-5.01 (m, 1H), 6.74-6.81 (m, 1H), 6.80 (d, J=15.3 Hz, 1H), 6.93 (d, J=8.7 Hz, 1H), 7.02 (d, CDCl<sub>3</sub> 1.8 Hz, 1H), 7.13 (dd, J=1.8, 8.4 Hz, 1H), 7.16-7.25 (m, 1H), 7.54 (s, 1H), 7.58 (d, J=15.6 Hz, 1H). MS (ESI<sup>+</sup>) (M+Na)<sup>+</sup> at m/z 552, 554.

#### Example 279

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(2-(methoxymethyl)tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 225, substituting ethyl nipecotate with 3-*N*-methoxymethyltetrazolylpiperidine, to give a light-yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.19 (d, *J* = 6.9 Hz, 6H), 1.62-1.80 (br m, 2H), 1.80-2.20 (br m, 2H), 2.20-2.39 (br m, 2H), 3.12-3.38 (br m, 2H), 3.46 (s, 3H), 4.11 (septet, *J* = 6.9 Hz, 1H), 4.17-4.34 (br m, 1H), 5.79 (s, 2H), 6.70 (br s, 1H), 7.05 (d, *J* = 15.3 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.35-7.68 (m, 5H), 8.42 (br s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 523.

10

Example 280

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(1-(methoxymethyl)tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 279 and separated from the same reaction mixture via SiO<sub>2</sub> flash column chromatography, to give a light-yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.19 (d, *J* = 6.9 Hz, 6H), 1.62-1.80 (br m, 2H), 1.80-2.20 (br m, 2H), 2.20-2.39 (br m, 2H), 3.12-3.38 (br m, 2H), 3.46 (s, 3H), 4.11 (septet, *J* = 6.9 Hz, 1H), 4.17-4.34 (br m, 1H), 5.79 (s, 2H), 6.70 (br s, 1H), 7.05 (d, *J* = 15.3 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.35-7.68 (m, 5H), 8.42 (br s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 523.

20

Example 281

SUB  
A69

(1-Methylindol-5-yl)[2-chloro-4-( E-((3-(1-pyrrolidin-2-onyl)propylamino)  
carbonyl)ethenyl) phenyl] sulfide

Example 281A

Triisopropylsilyl(1-methylindol-5-yl) sulfide

Sub<sup>5</sup>  
A69

To a stirred solution of 5-bromo-*N*-methyl indole (300 mg, 1.43 mmol) in 5 mL of benzene in a sealed tube was charged with Pd(PPh<sub>3</sub>)<sub>4</sub> (82 mg, 0.072 mmol), followed by KSTIPS (326 mg, 1.43 mmol). The mixture was flushed with N<sub>2</sub>, the tube was capped, and the reaction mixture refluxed for 2 h. The reaction mixture was then  
10 allowed to cool down, partitioned between Et<sub>2</sub>O and water. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The residue was purified on a SiO<sub>2</sub> flash column chromatography eluting with 5% EtOAc/hexanes to give 400 mg (88 %) of the title compound as colorless oil.

Example 281B

3-Chloro-4-((1-methylindol-5-yl)thio) benzaldehyde

15 To a stirred solution of thiolsilyl ether (1.0 g, 3.13 mmol) in 5 mL of DMF with 3-chloro-4-fluorobenzaldehyde (500 mg, 3.13 mmol) at ambient temperature was added CsF (5.7 mg, 0.38 mmol). The mixture was stirred over night before it was  
20 poured in water and extracted with Et<sub>2</sub>O (2×25 mL). The combined organic layer was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The residue

Sub  
A69  
was purified on a SiO<sub>2</sub> flash column chromatography eluting with 5-10 % EtOAc/hexanes to give 650 mg (71 %) of the title compound as white solid.

Example 281C

5      (1-Methylindol-5-yl)[2-chloro-4-( E-((3-(1-pyrrolidin-2-onyl)propylamino) carbonyl)ethenyl) phenyl] sulfide

10      The title compound was prepared by the procedures described in Example 92, substituting the benzoic acid with cinnamic acid prepared from the above-described aldehyde, and ammonium with 3-aminopropyl-1-pyrrolidin-2-one, to give a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.74 (br m, 2H), 2.07 (br m, 2H), 2.44 (br m, 2H), 3.32 (br m, 2H), 3.40 (br m, 4H), 3.85 (s, 3H), 6.36 (d, *J* = 15.3 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H), 7.36 (dd, *J* = 1.5, 9.0 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.50 (s, 1H), 7.89 (d, *J* = 1.5 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 468, 470. Anal. Calcd for C<sub>25</sub>H<sub>26</sub>ClN<sub>3</sub>O<sub>2</sub>S · 1.37 H<sub>2</sub>O: C, 60.95; H, 5.88; N, 8.53. Found: C, 60.97; H, 5.98; N, 8.46.

Example 282

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(tetrazol-5-yl) piperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20      The compound from Example 279 (75 mg, 0.14 mmol) was dissolved in 1 mL of neat TFA and left at ambient temperature for overnight. The reagent was then removed in vacuo and the residue was evaporated twice with benzene. The crude

product was purified using Gilson Preparative HPLC as described in Example 38B to give the title compound as a light-yellow solid (50 mg, 72 %); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.17 (d, *J* = 6.5 Hz, 6H), 1.25-1.39 (m, 1H), 1.69-1.81 (m, 1H), 2.09 (br s, 1H), 2.14-2.30 (m, 1H), 2.57-2.71 (m, 1H), 3.35-3.66 (m, 3H), 3.90-4.03 (m, 1H), 4.66-4.78 (m, 1H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 15.3 Hz, 1H), 7.32 (dd, *J* = 2.1, 6.9 Hz, 1H), 7.42 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.47-7.57 (m, 3H), 7.76 (d, *J* = 15.3 Hz, 1H), 8.46 (d, *J* = 2.1 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 479. Anal. Calcd for C<sub>24</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub>S · 0.28 H<sub>2</sub>O: C, 59.61; H, 5.54; N, 17.38. Found: C, 59.71; H, 5.44; N, 16.99.

#### Example 283

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 281C, substituting aminopropyl pyrrolidinone with ethyl nipecotate, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.26 (t, *J* = 7.5 Hz, 3H), 1.65-1.96 (m, 2H), 2.00-2.20 (m, 1H), 2.04 (s, 1H), 2.54 (br m, 1H), 3.12-3.34 (m, 1H), 3.85 (s, 3H), 3.92-4.07 (m, 1H), 4.07-4.20 (m, 1H), 4.15 (q, *J* = 7.5 Hz, 2H), 4.65-4.90 (m, 1H), 6.53 (d, *J* = 3.0 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 15.3 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H), 7.37 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.51 (s, 1H), 7.51 (d, *J* = 15.3 Hz, 1H), 7.89 (d, *J* = 1.5 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 483, 485.

Example 284

(1-Methylindol-5-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

5           The title compound was prepared by the procedures described in Example 155,  
substituting the ethyl ester from Example 137 with ethyl ester from Example 283, and  
KOH with NaOH, to provide a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.45-1.69  
(m, 1H), 1.69-1.98 (m, 2H), 1.98-2.22 (m, 1H), 2.51-2.70 (m, 1H), 3.05-3.47 (m, 1H),  
3.80-4.20 (m, 2H), 3.85 (s, 3H), 4.47-4.68 (m, 1H), 6.53 (d, *J* = 3.0 Hz, 1H), 6.57 (d, *J*  
10 = 8.1 Hz, 1H), 6.87 (d, *J* = 15.3 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 3.0 Hz,  
1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.51 (s, 1H), 7.52 (d, *J* = 15.3  
Hz, 1H), 7.89 (br s, 1H). MS (ESI<sup>+</sup>) (M-H+H)<sup>+</sup> at *m/z* 453, 455.

Example 285

15   (1-Methylindol-5-yl)[2-chloro-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the procedures described in Example  
281C, substituting aminopropyl pyrrolidinone with ethyl isonipecotate, giving a white  
solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.26 (t, *J* = 7.5 Hz, 3H), 1.64-1.83 (m, 2H), 1.88-  
20 2.08 (m, 2H), 2.48-2.67 (m, 1H), 2.86-3.40 (m, 2H), 3.85 (s, 3H), 3.89-4.24 (m, 1H),  
4.15 (q, *J* = 7.5 Hz, 2H), 4.24-4.65 (m, 1H), 6.53 (d, *J* = 3.0 Hz, 1H), 6.58 (d, *J* = 8.1  
Hz, 1H), 6.81 (d, *J* = 15.3 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H),

7.37 (dd,  $J = 1.5, 9.0$  Hz, 1H), 7.50 (d,  $J = 9.0$  Hz, 1H), 7.50 (d,  $J = 15.3$  Hz, 1H), 7.88 (d,  $J = 1.5$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  483, 485.

Example 286

(1-Methylindol-5-yl)[2-chloro-4-(*E*-(3-carboxypiperidin-1-yl)carbonyl)ethenyl  
phenyl] sulfide

The title compound was prepared by the procedures described in Example 155, substituting the ethyl ester from Example 137 with ethyl ester from Example 285, and KOH with NaOH, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.60-1.90 (m, 2H), 1.90-2.10 (m, 2H), 2.57-2.72 (m, 1H), 2.80-3.40 (m, 2H), 3.85 (s, 3H), 3.91-4.20 (m, 1H), 4.30-4.68 (m, 1H), 6.53 (d,  $J = 3.0$  Hz, 1H), 6.57 (d,  $J = 8.1$  Hz, 1H), 6.80 (d,  $J = 15.3$  Hz, 1H), 7.07 (d,  $J = 8.1$  Hz, 1H), 7.15 (d,  $J = 3.0$  Hz, 1H), 7.37 (dd,  $J = 1.5, 9.0$  Hz, 1H), 7.51 (d,  $J = 9.0$  Hz, 1H), 7.51 (s, 1H), 7.51 (d,  $J = 15.3$  Hz, 1H), 7.89 (br s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  455, 457. Anal. Calcd for C<sub>24</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>3</sub>S · 0.42 H<sub>2</sub>O: C, 62.32; H, 5.20; N, 6.06. Found: C, 62.35; H, 5.30; N, 5.87.

Example 287

(2-Isopropylphenyl)[2-nitro-4-(*E*-(2-(1-methylpyrrolidin-2-yl)ethylamino)carbonyl)ethenyl phenyl] sulfide

The title compound was prepared according to the procedures of Example 1. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  8.44 (d, 1H,  $J = 1.8$  Hz), 7.56 (d, 1H,  $J = 3.7$  Hz), 7.50-7.58 (m, 3H), 7.43 (DD, 1H,  $J = 1.84, 8.4$  Hz), 7.30 (dd, 1H,  $J = 2.2, 6.8$  Hz),

6.78 (d, 1H, J = 8.5 Hz), 6.52 (d, 1H, J = 15.8 Hz), 3.63 (m, 2H), 3.42 (m, 3H), 3.00 (m, 1H), 3.78 (m, 1H), 2.59 (s, 3H), 2.05 (m, 1H), 2.00 (m, 5H), 1.18 (d, 6H, J = 7.0 Hz). MS (ESI)  $m/z$  454, 490.

5

Example 288

(2-Isopropylphenyl)[2-nitro-4-(E-((4-(pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.43 (d, 1H, J = 1.8 Hz), 7.57 (d, 1H, J = 8.5 Hz), 7.51-  
10 7.55 (m, 3H), 7.41 (dd, 1H, J = 1.84, 8.8 Hz), 7.31 (dd, 1H, J = 2.4, 7.5 Hz), 6.92 (d,  
1H, J = 15.4 Hz), 6.70 (d, 1H, J = 8.5 Hz), 4.70 (m, 1H), 4.10 (m, 1H), 3.44 (pent, 1H,  
J = 6.8 Hz), 3.16 (m, 1H), 2.80 (br, 4H), 2.55 (br, 1H), 2.03 (m, 4H), 1.90 (m, 4H),  
1.65 (m, 1H), 1.18 (d, 6H, J = 7.0 Hz). MS (ESI)  $m/z$  480, 959.

15

Example 289

(2-Isopropylphenyl)[2-nitro-4-(E-((4-sulfopiperidin-1-yl)carbonyl)ethenyl) phenyl]  
sulfide

The title compound was prepared according to the procedures of Example 1.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.63 (d, 1H, J = 1.8 Hz), 7.92 (dd, 1H, J = 1.8, 8.8  
20 Hz), 7.60 (m, 3H), 7.47 (d, 1H, J = 14.2 Hz), 7.42 (d, 1H, J = 14.2 Hz), 6.62 (d, 1H, J  
= 8.5 Hz), 4.45 (m, 2H), 4.38 (m, 2H), 3.34 (m, 1H), 3.00 (m, 2H), 2.70 (m, 1H), 2.60  
(m, 2H), 1.14 (d, 6H, J = 6.9 Hz). MS (ESI)  $m/z$  491, 981.

Example 290

(2-Isopropylphenyl)[2-nitro-4-(*E*-((3-hydroxypiperidin-1-yl)carbonyl)ethenyl) phenyl]  
sulfide

5           The title compound was prepared according to the procedures of Example 1.  
  
      <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.43 (s, 1H), 7.50-7.62 (m, 4H), 7.41 (d, 1H, J = 8.1  
Hz), 6.97 (m, 1H), 6.69 (d, 1H, J = 8.1 Hz), 3.85 (m, 2H), 3.65 (m, 1H), 3.50 (m, 3H),  
1.93 (m, 2H), 1.65 (m, 2H), 1.18 (d, 6H, J = 6.6 Hz). MS (ESI) *m/z* 427, 449, 853,  
875.

10

Example 291

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-  
((ethanesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

      The title compound was prepared by the procedures described in Example 227.

15       The product was purified by reversed-phase HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ  
1.34 (t, J= 7.0 Hz, 2H), 1.44 (t, J=7.0 Hz, 3H), 1.95 (br, 1/2H), 2.20 (br, 1/2H), 2.68  
(br, 1H), 3.14 (q, J=7.0 Hz, 2H), 3.45 (m, 1H), 3.65 (m, 1H), 3.93 (m, 1H), 4.30 (m,  
4H), 4.50-4.60 (br, 2H), 6.92 (d, J=8.0 Hz, 1H), 6.98-7.04 (m, 3H), 7.06 (m, 1H), 7.40  
(d, J=8.0 Hz, 1H), 7.65 (m, 1H), 7.75 (s, 1H). MS (APCI) *m/z* 585 (M+H)<sup>+</sup>.

20

Example 292

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-((*p*-toluenesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the same procedure described in Example

229. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.25 (m, 2H), 1.55 (m, 1H), 1.70-2.25 (br, 1H),  
 2.41 (d, J=13.0 Hz, 3H), 2.55 (br, 1H), 3.50-3.80 (br, 2H), 4.20-4.35 (m, 4H), 4.68-  
 4.75 (m, 2H), 6.90 (d, J=8.0 Hz, 1H), 7.00-7.10 (m, 2H), 7.30 (d, J=8.0 Hz, 1H), 7.81  
 (d, J=8.0 Hz, 1H), 7.91 (m, 1H). MS (CI/NH<sub>3</sub>) m/z 647 (M+H)<sup>+</sup>. Anal. calcd. for  
 C<sub>31</sub>H<sub>29</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub> • 0.5 H<sub>2</sub>O: C, 56.78; H, 4.61; N, 4.27. Found: C, 56.86; H, 4.69; N,  
 4.35.

Example 293

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((4-((ethanesulfonylamino)carbonyl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 227,

giving a white foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.35-1.40 (m, 2H), 1.44 (t, J=7.0  
 Hz, 3H), 1.76 (m, 1H), 2.0 (m, 1H), 2.50-3.20 (br, 1H), 3.15 (q, J=7.0 Hz, 2H), 3.40-  
 3.55 (m, 2H), 4.25-4.32 (m, 4H), 4.52 (br, 2H), 6.90 (d, J=8.0 Hz, 1H), 6.98-7.05 (dd,  
 J=2.0, 8.0 Hz, 2H), 7.06 (d, J=2.0 Hz, 1H), 7.40 (m, 1H), 7.60 (m, 1H), 7.75 (s, 1H),  
 8.22 (br, 1H). MS (APCI) m/z 585 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>26</sub>H<sub>27</sub>F<sub>3</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub> • 0.8  
 H<sub>2</sub>O: C, 52.13; H, 4.81; N, 4.68. Found: C, 52.14; H, 4.80; N, 4.66.

Example 294

SJN  
A72

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A72

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((2(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The corresponding nitrile (160 mg, 0.336 mmol, prepared via the procedures of Example 1), sodium azide (56.6 mg, 0.872 mmol), n-Bu<sub>3</sub>SnCl and THF were mixed in a reaction tube, flushed with nitrogen and heated to reflux overnight. The mixture was then cooled to ambient temperature, and 1N HCl soln. was added. The mixture was extracted with ethyl acetate three times and the combined organics were dried over MgSO<sub>4</sub>. The mixture was filtered through a short silica gel plug to give 96 mg (56% yield) of the desired material. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz, 100 °C) δ 7.99 (d, 1H, J = 1.7 Hz), 7.79 (dd, 1H, J = 2.0, 8.6 Hz), 7.50 (d, 1H, J = 15.3 Hz), 7.24 (d, 1H, J = 15.6 Hz), 7.14 (d, 1H, J = 8.2 Hz), 6.96 (m, 1H), 6.94 (d, 1H, J = 2.1 Hz), 6.92 (m, 1H), 4.60 (dd, 1H, J = 3.0, 9.8 Hz), 4.50 (br d, 1H, J = 12.2 Hz), 4.26 (m, 5H), 4.17 (m, 1H), 4.00 (dt, 1H, J = 3.2, 11.6 Hz), 3.72 (td, 1H, J = 3.0, 11.0 Hz), 3.43 (br m, 1H), 3.29 (br m, 1H). MS (ESI) m/z -518. Anal. Calcd for C<sub>23</sub>H<sub>20</sub>F<sub>3</sub>N<sub>5</sub>O<sub>4</sub>S · 1.83 HOAc: C, 50.88; H, 4.38; N, 11.13. Found: C, 50.61; H, 4.46; N, 11.4.

#### Example 295

(2-Isopropylphenyl)[2-nitro-4-(E-((2-butyl, 5-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20

#### Example 295A

2-Butyl-5-cyanomorpholine

The title compound was prepared by the procedures described in Example 260A, substituting ethanolamine with 2-aminohexanol.

### Example 295B

5 (2-Isopropylphenyl)[2-nitro-4-( E-((2-butyl-5-cyanomorpholin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the procedures described in Example 260B, substituting the morpholine from Example 260A with the compound of Example 295A.

### Example 295C

(2-Isopropylphenyl)[2-nitro-4-( E-((2-butyl-5-(tetrazol-5-yl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 262, substituting the nitrile compound from Example 260 with the compound of Example 295B, giving a light-yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 3:2 mixture of diastereomers) δ 0.89 (t, *J* = 7.5 Hz, 1H), 1.01 (br m, 1H), 1.19 (d, *J* = 6.5 Hz, 6H), 1.23-1.43 (m, 4H), 1.68-1.84 (m, 1H), 3.10-3.61 (m, 2H), 3.83-4.17 (m, 2H), 4.40-5.26 (m, 2H), 6.67-6.77 (m, 1H), [6.91 (d), 7.02 (d), *J* = 15.3 Hz, 1H in total], 7.25-7.37 (m, 2H), 7.44-7.60 (m, 3H), [7.67 (d), 7.79 (d), *J* = 15.3 Hz, 1H in total], 8.43-8.50 (m, 1H). MS (ESI<sup>+</sup>) (M-H)<sup>+</sup> at *m/z* 535.

Example 296

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

5

Example 296A

Triisopropylsilyl (2-(and 3-)hydroxymethylbenzodioxan-6-yl) sulfide

The title compound was prepared by the procedures described in Example 281A, substituting 5-bromo-*N*-methyl indole with a mixture of 6-bromo-2-hydroxymethylbenzenedioxane and 6-bromo-3-hydroxymethylbenzenedioxane.

10

Example 296B

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-( E-((4-acetylpiperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example

15 281B, substituting 3-chloro-4-fluorobenzaldehyde with 4-chloro-3-nitrocinnamide, giving a light yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 3:2 mixture of diastereomers) δ [2.11 (s), 2.15 (s), 3H in total], 3.48-3.83 (m, 8H), 3.83-4.04 (m, 2H), 4.20 (dd, *J* = 8.4, 11.4 Hz, 1H), 4.26-4.44 (m, 2H), 6.89 (d, *J* = 5.7 Hz, 1H), 6.92 (s, 1H), 6.97-7.11 (m, 1H), 7.04 (d, *J* = 15.0 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 7.46 (br d, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 15.0 Hz, 1H), 8.41 (d, *J* = 2.1 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 500.

20

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SUM  
A73

Example 297

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example

- 5 296B, substituting the acetyl piperazine 4-chloro-3-nitrocinnamide with 3-aminopropyl-1-pyrrolidin-3-one 4-chloro-3-nitrocinnamide, giving a light-yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 3:2 mixture of diastereomers) δ 1.75 (br m, 2H), 2.08 (p, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 3.27-3.48 (m, 6H), 3.82-4.03 (m, 2H), 4.13-4.44 (m, 3H), 6.49 (d, *J* = 15.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), [6.99 (d), 10 7.01 (d), *J* = 8.4 Hz, 1H in total], [7.06 (dd), 7.08 (dd), *J* = 1.5, 2.4 Hz, 1H in total], [7.13 (d), 7.14 (d), *J* = 2.4 Hz, 1H in total], 7.17 (br s, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 15.0 Hz, 1H), 8.36 (d, *J* = 1.5 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 514.

Example 298

(2-(and 3-)(Hydroxymethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 281,

- substituting 6-thiolsilyl indole with the thiolsilyl ether described in Example 296A, and 3-chloro-4-fluorobenzaldehyde with 4-fluoro-3-trifluoromethylbenzaldehyde, 20 producing a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 3:2 mixture of diastereomers) δ 1.75 (br m, 2H), 2.09 (br m, 2H), 2.45 (br m, 2H), 3.25-3.60 (m, 6H), 3.80-4.43 (m, 5H), 6.46 (d, *J* = 15.3 Hz, 1H), [6.92 (d), 6.95 (d), *J* = 6.8 Hz, 1H in total], [7.03 (d),

7.04 (d),  $J = 8.1$  Hz, 1H in total], 7.06-7.10 (m, 1H), 7.13 (br s, 1H), 7.42 (d,  $J = 8.1$  Hz, 1H), 7.54 (d,  $J = 15.3$  Hz, 1H), 7.77 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  537.

### Example 299

5 (3-Hydroxymethyl)-benzodioxan-6-yl)[2-nitro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

### Example 299A

#### 3-(Hydroxymethyl)-6-bromo-benzodioxane

10 To a stirred solution of 5-bromosalicylaldehyde (5.0 g, 24.9 mmol), and epichlorohydrin (5.6 mL, 72.1 mmol) in 20 mL of DMF at 80 °C was added K<sub>2</sub>CO<sub>3</sub> slowly in portions. The resulting mixture was then heated at 90 °C for 3 h. Reaction was then stopped, water was added, extracted with diethyl ether. The organic extracts were washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The residue  
15 was purified on a SiO<sub>2</sub> flash column chromatography eluting with 15-30 % EtOAc/hexanes to give 2.82 g (44 %) of the title compound as colorless oil.

To a stirred solution of the aldehyde (2.82 g, 11 mmol) in 35 mL of CHCl<sub>3</sub>, was added mCPBA (2.27 g, 13 mmol). The mixture was stirred at ambient temperature for 30 min and then heated at 50 °C for 2 h. The reaction was then  
20 quenched with aq. Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub>, extracted with Et<sub>2</sub>O (2×50 mL). The combined organic layer was washed with aq. NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo

Sub  
A76  
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Sub A76  
to give 2.92 g of crude product which was proceeded to the next step without purification.

To a stirred solution of the above-described crude formate (2.92 g) in 5 mL of THF was added 3N aq. NaOH (3.9 mL, 11.7 mmol). The reaction mixture was then heated at 70 °C for 4 h. The reaction mixture was then partitioned between EtOAc and water. The organic layer was then washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo to give 2.50 g (93% over two steps) of the title compound.

#### Example 299B

10

#### Triisopropyl (3-(hydroxymethyl)-benzodioxan-6-yl) sulfide

The title compound was prepared by the procedures described in Example 281A, substituting 5-bromo-*N*-methyl indole with the bromide from Example 299A.

#### Example 299C

#### (3-Hydroxymethyl)-benzodioxan-6-yl][2-nitro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Sub A77  
The title compound was prepared by the procedures described in Example 297, substituting the mixture of thiolsilyl ethers from Example 296A with the compound of Example 299B, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.74 (br m, 2H), 2.08 (t, *J* = 7.5 Hz, 2H), 2.44 (t, *J* = 7.5 Hz, 2H), 3.25-3.53 (m, 6H), 3.88 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.97 (dd, *J* = 4.8, 16.8 Hz, 1H), 4.21 (dd, *J* = 3.1, 12.9 Hz, 1H), 4.26-4.36 (m, 1H), 4.40 (dd, *J* = 2.4, 12.9 Hz, 1H), 6.49 (d, *J* = 15.3 Hz, 1H), 6.88 (d, *J* =

8.7 Hz, 1H), 7.00 (d,  $J = 8.7$  Hz, 1H), 7.07 (dd,  $J = 2.4, 8.7$  Hz, 1H), 7.14 (d,  $J = 2.4$  Hz, 1H), 7.20 (br s, 1H), 7.46 (dd,  $J = 0.9, 8.7$  Hz, 1H), 7.54 (d,  $J = 15.3$  Hz, 1H), 8.36 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  514. Anal. Calcd for C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>O<sub>7</sub>S · 0.82 H<sub>2</sub>O: C, 56.83; H, 5.46; N, 7.95. Found: C, 56.84; H, 5.18; N, 7.74.

5

Example 300

(Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the procedures described in Example 263,  
10 substituting 4-fluoro-3-trifluoromethylbenzaldehyde with 3-chloro-4-  
fluorobenzaldehyde, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.64-1.88 (br  
m, 2H), 1.95-2.09 (br m, 2H), 2.57-2.73 (m, 1H), 2.90-3.17 (m, 1H), 3.17-3.50 (m,  
1H), 3.90-4.19 (m, 1H), 4.25-4.36 (m, 4H), 4.39-4.66 (m, 1H), 6.75 (d,  $J = 8.4$  Hz,  
1H), 6.84 (d,  $J = 15.3$  Hz, 1H), 6.93 (d,  $J = 8.7$  Hz, 1H), 7.03 (dd,  $J = 2.4, 8.7$  Hz,  
15 1H), 7.08 (d,  $J = 2.4$  Hz, 1H), 7.18 (d,  $J = 8.4$  Hz, 1H), 7.51 (s, 1H), 7.54 (d,  $J = 15.3$   
Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  460, 462.

Example 301

(2-(and 3-)(Aminomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-(pyrrolidin-  
2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

20

Sub  
A78Example 301A

(2-(and 3-)(Mesyloxymethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

To a stirred solution of alcohol from Example 298 (200 mg, 0.37 mmol) in 2 mL of methylene chloride with Et<sub>3</sub>N (104 mL, 0.74 mmol) was added

5 methanesulfonyl chloride (35 mL, 0.56 mmol) dropwise. The mixture was then stirred at ambient temperature for one hour. The reaction mixture was then poured into 3N HCl, extracted with EtOAc (2×10 mL). The combined organic layer was washed with aq. NaHCO<sub>3</sub>, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo to give 275 mg of crude product which was proceeded to the next step without purification.

10

#### Example 301B

(2-(and 3-)(Azidomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

To a stirred solution suspension of NaN<sub>3</sub> (44 mg, 0.68 mmol) in 1 mL of

15 DMSO was added mesylate (275 mg) in 0.5 mL of DMSO solution. The reaction mixture was then heated at 70 °C for 2 h, then cooled down to room temperature, water was added, extracted with EtOAc (2×10 mL). The combined organic layer was washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The residue was purified on a SiO<sub>2</sub> flash column chromatography eluting with 5-10% MeOH/EtOAc to

20 give 35 (17%, two steps) mg of the title compound as light brown oil.

Example 301C

(2-(and 3-)(Aminomethyl)-benzodioxan-6-yl)[2-trifluoromethyl-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

Sub  
A80  
5 To a stirred solution of azide (230 mg, 0.41 mmol) in 1 mL of THF was added PPh<sub>3</sub> (118 mg, 0.45 mmol), followed by one drop of water. The mixture was then stirred at room temperature for one hour. The volatile solvent was then removed in vacuo and the crude product was purified using Gilson Preparative HPLC as described in Example 38B to give 25 mg (11%) of the title compound. Light brown oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, 3:2 mixture of diastereomers) δ 1.74 (br m, 2H), 1.96-2.16 (m, 2H), 2.35-2.50 (m, 2H), 3.23-3.47 (m, 6H), 3.92-4.63 (m, 5H), 6.41-6.55 (m, 1H), 6.83-7.10 (m, 3H), 7.36-7.58 (m, 3H), 7.67-7.67 (m, 2H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at m/z 536. Anal. Calcd for C<sub>26</sub>H<sub>28</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub>S · 0 H<sub>2</sub>O: C, 58.31; H, 5.27; N, 7.85. Found: C, 58.34; H, 5.48; N, 7.78.

15

Example 302

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(methylaninocarbonyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.6 Hz, 6H); 2.61 (d, J = 4.8 Hz, 3H); 3.14-4.62 (br m, 7H); 3.30-3.40 (m, 1H); 6.63 (d, J = 8.8 Hz, 1H); 7.32-7.62 (m, 6H); 7.80-7.97 (m, 2H); 8.66(d, J = 1.5 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 470.

Anal calcd for  $C_{24}H_{27}N_3S_1O_5 \cdot 0.8H_2O$ : C, 59.58; H, 5.96; N, 8.68. Found: C, 59.57; H, 5.94; N, 8.72.

### Example 303

5        (2-Isopropylphenyl)[2-nitro-4-( E-((3-(hydroxymethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 2.70-3.51 (br m, 5H); 3.30-3.40 (m, 1H); 3.83-3.93 (m, 1H); 4.03-4.47 (br m, 2H); 4.74-4.82 (m, 1H); 6.64 (d, J = 8.5 Hz, 1H); 7.30-7.62 (m, 6H); 7.86-7.94 (m, 1H); 8.59-8.65 (m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 443. Anal calcd for  $C_{23}H_{26}N_2S_1O_5$ : C, 62.43; H, 5.92; N, 6.33. Found: C, 62.12; H, 6.20; N, 6.06.

### Example 304

15        (2-Isopropylphenyl)[2-nitro-4-( E-((3-(acetoxymethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.1 Hz, 6H); 2.04 (s, 3H); 3.30-3.40 (m, 1H); 2.58-4.41 (br m, 9H); 6.64 (d, J = 8.5 Hz, 1H); 7.30-7.62 (m, 6H); 7.90 (dd, J = 8.5, 1.8 Hz, 1H); 8.59-8.65 (m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 485. Anal calcd for  $C_{25}H_{28}N_2S_1O_6$ : C, 61.97; H, 5.82; N, 5.78. Found: C, 61.85; H, 5.84; N, 5.68.

Example 305

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(aminomethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

5 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 2.61 (d, J = 5.5 Hz, 2H); 2.49-3.60 (br m, 5H); 3.82-3.93 (m, 1H); 4.13-4.45 (m, 2H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.62 (m, 6H); 7.88-7.95 (m, 1H); 8.59-8.67(m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 442. Anal calcd for C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>·0.4H<sub>2</sub>O: C, 61.55; H, 6.25; N, 9.36. Found: C, 61.60; H, 6.25; N, 9.00.

10

Example 306

(2-Isopropylphenyl)[2-nitro-4-( E-((3-(acetamidomethyl)morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.82 (s, 3H); 2.70-3.50 (br m, 7H); 3.85-3.94 (m, 1H); 4.13-4.40 (m, 2H); 6.64 (d, J = 8.5 Hz, 1H); 7.32-7.62 (m, 6H); 7.88-8.06 (m, 1H); 8.59-8.67(m, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 484. Anal calcd for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>5</sub>·0.27H<sub>2</sub>O: C, 61.47; H, 6.10; N, 8.60. Found: C, 61.50; H, 6.34; N, 8.53.

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Example 307

(Benzodioxan-6-yl)[2-chloro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 300 substituting ethyl isonipecotate with N-(3'-aminopropyl)-2-pyrrolidinone. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.75 (br s, 2H), 2.02-2.34 (m, 2H), 2.40-2.50 (m, 2H), 3.30-3.50 (m, 6H), 4.28-4.33 (m, 4H), 6.40 (br, 1H), 6.75 (d, J=8.0 Hz, 1H), 6.93 (d, J=8.5 Hz, 1H), 7.02 (dd, J=2.0, 8.0 Hz, 1H), 7.08 (d, J=2.0 Hz, 1H), 7.18 (d, J=8.5 Hz, 1H), 7.45 (m, 1H), 7.50 (s, 1H). MS (ESI) m/z 473 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>24</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>4</sub>S•0.5 H<sub>2</sub>O: C, 59.81; H, 5.44; N, 5.81. Found: C, 59.76; H, 5.80; N, 5.43.

### Example 308

(Benzodioxan-6-yl)[2-chloro-4-(E-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 300 substituting ethyl isonipecotate with ethyl nipecotate. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.25 (t, J=7.0 Hz, 3H), 1.60-1.90 (br, 2H), 2.10 (br, 1H), 2.52 (br, 1H), 3.00-3.50 (br, 2H), 3.80 (br, 1H), 4.10-4.20 (m, 4H), 4.28-4.35 (m, 4H), 6.74 (d, J=8.0 Hz, 1H), 6.92 (d, J=8.0 Hz, 1H), 7.02 (dd, J=2.0, 8.0 Hz, 1H), 7.08 (d, J=2.0 Hz, 1H), 7.18 (m, 1H), 7.50-7.03 (m, 3H). MS (ESI) m/z 488 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>25</sub>H<sub>26</sub>ClNO<sub>5</sub>SN<sub>a</sub>•0.5 H<sub>2</sub>O: C, 60.42; H, 5.48; N, 2.82. Found: C, 60.61; H, 5.51; N, 2.42.

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Example 309

(Benzodioxan-6-yl)[2-chloro-4-( E-((2-carboethoxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by the same procedure described in Example

- 5 300 substituting ethyl isonipecotate with ethyl pipercolinate. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300  
MHz) δ 1.30 (t, J=7.0 Hz, 3H), 1.30-1.50 (br, 3H), 1.55-1.85 (br, 3H), 2.30 (m, 1H),  
4.00 (m, 1H), 4.20 (m, 2H), 4.30 (m, 4H), 5.44 (br, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.90  
(d, J=8.0 Hz, 1H), 7.00 (dd, J=2.0, 8.0 Hz, 1H), 7.07 (d, J=2.0 Hz, 1H), 7.10-7.20 (m,  
2H), 7.22 (m, 1H), 7.50 (s, 1H). MS (ESI) m/z 488 (M+H)<sup>+</sup>. Anal. calcd. for  
10 C<sub>25</sub>H<sub>26</sub>ClNO<sub>5</sub>S: C, 61.53; H, 5.37; N, 2.87. Found: C, 61.86; H, 5.63; N, 2.56.

Example 310

(2-Methoxyphenyl)-[2,3-dichloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]  
sulfide

Example 310A

2,3-Dichloro-4-trifluoromethanesulfonyloxy-benzaldehyde

- 2,3-Dichloro-4-hydroxy-benzaldehyde (9.10 g., J. Med. Chem. 19 (4), 534,  
1994) was dissolved in 45 ml. pyridine at room temperature. The solution was placed  
20 in an ice bath and immediately, 15.63 g. of trifluoromethanesulfonic anhydride was  
added slowly. [Note: If the pyridine solution is cooled to zero before addition of  
triflic anhydride the aldehyde crystallizes out and the mixture cannot be stirred.]

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After the addition is complete the dark mixture was stirred for 1 hour at room temperature. It was then poured into a stirred mixture of ice water, 100 ml. of concentrated HCl and ether. [Note: Not everything is soluble in this mixture] The ether layer was separated, dried over sodium sulfate, and the solvent removed. Warm

5 heptane was added to this residue, and any insoluble material was filtered. The solution was concentrated to give 8.74 g. (57% yield) of product as an orange oil which solidified in the refrigerator.

#### Example 310B

10

#### 2,3-Dichloro-4-(2-methoxyphenylthio)-benzaldehyde

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2,3-Dichloro-4-trifluoromethanesulfonyloxy-benzaldehyde (2.50 g.) was dissolved in 6 ml. acetonitrile. 2-Methoxybenzenethiol (2.55 g. of 70% pure material, 50% excess) was added. With cooling 2.50 g. diisopropylethylamine was added slowly. The solution was removed from the ice bath, whereon a solid formed. The

15 solution was warmed in a 50C waterbath for 5 minutes. More acetonitrile (5 ml.) was added and the mixture was cooled in ice, and then filtered to get 2.047 g. of product, m.p. 137-139C.

#### Example 310C

20

#### 2,3-Dichloro-4-(2-methoxyphenylthio)-cinnamic acid

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A mixture of 2,3-dichloro-4-(2-methoxyphenylthio)-benzaldehyde (2.03 g.), 1.44 g. malonic acid, 5 ml. pyridine, and 0.100 g piperidine was heated to 115 degrees

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for 1.5 hours. The mixture was cooled, and ice and HCl were added. The resulting solid was filtered, washed with water and dissolved in tetrahydrofuran. This solution was dried over sodium sulfate, the solvent removed and ether added to give 1.733 g of product, m.p. 187-188C.

5

Example 310D

(2-Methoxyphenyl)-[2,3-dichloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]

sulfide

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A85

The title compound was prepared according to the procedure of Example 1, substituting the cinnamic acid of Example 310C, giving a white solid, m.p. 161-162C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.83 (s, 3H), 6.55 (d, J=9Hz, 1H), 6.70 (broad d, J=15 Hz, 1H), 6.99-7.05 (m, 2H), 7.26 (d, J=9 Hz, 1H), 7.43-7.50 (m, 2H), 8.07 (broad d, J=15 Hz, 1H) Anal. Calcd. for C<sub>20</sub>H<sub>19</sub>Cl<sub>2</sub>NO<sub>3</sub>S: C, 56.61; H, 4.51; N, 3.30. Found: C, 56.75; H, 4.57; N, 2.61.

10

15

Example 311

(2-Methoxyphenyl)-[2,3-dimethyl-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]

sulfide

The title compound was prepared according to the procedures of Example 310.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.39 (s, 3H), 2.42 (s, 3H), 3.60-3.80 (m, 8H), 3.90 (s, 3H), 6.69 (d, J=15 Hz, 1H), 6.82-6.94 (m, 3H), 7.05 (d, J=9Hz, 1H), 7.20-7.30 (m,

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2H), 8.06 (d, J=15 Hz, 1H). Anal. Calcd. for  $C_{22}H_{25}NO_3S$ : C, 68.91; H, 6.57; N, 3.65. Found: C, 68.75; H, 6.67; N, 3.24.

### Example 312

5 (2-Isopropylphenyl)[2-nitro-4-(*E*-((indol-5-ylamino)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 1.

$^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  11.04 (s, 1H), 10.10 (s, 1H), 8.52 (d, 1H, J = 1.5 Hz), 8.02 (s, 1H), 7.81 (dd, 1H, J = 1.8, 8.5 Hz), 7.53-6.63 (m, 4H), 7.39 (m, 1H), 7.25-7.35 (m, 3H), 6.94 (d, 1H, J = 15.8 Hz), 7.72 (d, 1H, J = 8.5 Hz), 6.40 (m, 1H), 3.33  
10 (m, 1H), 1.16 (d, 6H, J = 6.6 Hz). MS (ESI)  $m/z$  458, 480, 915. Anal. Calcd for  $C_{26}H_{23}N_3O_3S \cdot 0.22 H_2O$ : C, 67.67; H, 5.12; N, 9.10. Found: C, 67.68; H, 5.19; N, 9.08.

### Example 313

15 (Benzodioxan-6-yl)[2-chloro-4-(*E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by hydrolysis of the compound of Example 308 under basic condition (aq. NaOH/EtOH).  $^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  1.10-1.40 (m, 2H), 1.60 (m, 1H), 1.76-1.96 (m, 3H), 2.88 (m, 1H), 3.98 (m, 1H), 3.98 (m,  
20 1H), 4.30 (m, 4H), 6.72 (d, J=8.0 Hz, 1H), 7.02 (m, 3H), 7.30 (m, 2H), 7.48 (m, 1H), 7.92 (m, 1H). MS (ESI)  $m/z$  458 (M+H) $^+$ . Anal. calcd. for  $C_{23}H_{21}ClNO_5SNa$ : C, 55.76; H, 4.58; N, 2.83. Found: C, 55.76; H, 4.78; N, 2.63.

## Example 314

(Benzodioxan-6-yl)[2-chloro-4-( E-((3-(tetrazol-5-yl)piperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

- 5        The title compound was prepared by the procedures described in Example 282, producing a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.66-1.80 (m, 2H), 2.10-2.30 (m, 2H), 2.64 (m, 1H), 3.55 (m, 2H), 3.98 (m, 1H), 4.25 (m, 1H), 4.30-4.36 (m, 4H), 6.72 (dd, J=3.0, 12.0 Hz, 2H), 6.93 (d, J=8.0 Hz, 1H), 7.03 (dd, d=2.0, 8.0 Hz, 1H), 7.09 (d, J=2.0 Hz, 1H), 7.20 (d, J=8.5 Hz, 1H), 7.52 (s, 1H), 7.70 (d, J=15.0 Hz, 1H).
- 10      MS (ESI) m/z 484 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>23</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>3</sub>S•0.38 H<sub>2</sub>O: C, 56.28; H, 4.67; N, 14.27. Found: C, 56.46; H, 4.58; N, 13.94.

## Example 315

(Benzodioxan-6-yl)[2-chloro-4-( E-((4-(tert-butoxycarbonyl)piperazin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide

- 15        The title compound was prepared by the procedures described in Example 300 substituting ethyl isonipecotate with 1-Boc-piperazine. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.50 (s, 9H), 3.50 (br, s 4H), 3.70 (br, 4H), 4.28-4.35 (m, 4H), 6.74 (d, J=8.0 Hz, 1H), 6.82 (m, 1H), 6.92 (d, J=8.0 Hz, 1H), 7.02 (dd, J=2.0, 8.0 Hz, 1H), 7.17 (d, J=2.0 Hz, 1H), 7.28 (d, J=8.0 Hz, 1H), 7.50 (s, 2H), 7.58 (m, 1H). MS (ESI) m/z 517 (M+H)<sup>+</sup>.
- 20        Anal. calcd. for C<sub>26</sub>H<sub>29</sub>ClN<sub>2</sub>O<sub>5</sub>S•0.1 H<sub>2</sub>O: C, 60.19; H, 5.67; N, 5.40. Found: C, 60.20; H, 5.97; N, 5.11.

Example 316

(Benzodioxan-6-yl)[2-chloro-4-( E-((2-carboxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

The title compound was prepared by hydrolysis of the compound of Example  
5 309 under basic conditions (aq. NaOH/EtOH). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ  
1.10-1.40 (m, 3H), 1.45-1.60 (m, 2H), 2.25-2.45 (m, 2H), 2.55-2.80 (m, 1H), 4.30 (m,  
4H), 4.50 (m, 1H), 6.70 (d, J=8.0 Hz, 1H), 7.00 (m, 3H), 7.10 (m, 1H), 7.25 (d, J=16.0  
Hz, 1H), 7.48 (d, J=8.0 15.5 Hz, 1H), 7.90 (d, J=15.5 Hz, 1H). MS (ESI) m/z 458  
(M+H)<sup>+</sup>. Anal. calcd. for C<sub>23</sub>H<sub>21</sub>ClNO<sub>5</sub>SNa•1.3 H<sub>2</sub>O: C, 54.69; H, 4.73; N, 2.45.  
10 Found: C, 54.67; H, 4.71; N, 2.77.

Example 317

(Benzodioxan-6-yl)[2-chloro-4-( E-((3-(tetrazol-5-yl)morpholin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide

15 The title compound was prepared by the procedures described in Example 262.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.50-1.70 (m, 2H), 3.15 (br, 1H), 3.70-3.90 (m, 2H),  
4.25-4.35 (m, 4H), 4.55 (m, 1H), 5.04 (br, 1H), 6.72 (d, J=8.0 Hz, 1H), 6.93 (d, J=8.0  
Hz, 1H), 7.03 (dd, J=2.0, 8.0 Hz, 1H), 7.07 (d, J=2.0 Hz, 1H), 7.20-7.30 (m, 2H), 7.50  
(m, 1H), 7.65 (m, 1H). MS (ESI) m/z 486 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>22</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>4</sub>S  
20 •H<sub>2</sub>O: C, 52.43; H, 4.40; N, 13.90. Found: C, 52.34; H, 4.35; N, 13.62.

Example 318

(Benzodioxan-6-yl)[2-chloro-4-(E-((4-(methylaminocarbonyl)piperazin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by deprotection of the of Example 315 compound using anhydrous TFA in dichloromethane, followed by treatment with methyl isocyanate. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.88 (s, 3H), 3.50 (br, 4H), 3.72 (br, 4H), 4.30 (m, 4H), 6.74 (d, J=8.0 Hz, 1H), 6.82 (d, J=15.0 Hz, 1H), 6.92 (d, J=8.0 Hz, 1H), 7.03 (dd, J=2.0, 8.0 Hz, 1H), 7.08 (d, J=2.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 7.50 (s, 1H), 7.60 (m, 1H). MS (ESI) m/z 474 (M+H)<sup>+</sup>. Anal. calcd. for C<sub>23</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>4</sub>S: C, 57.63; H, 5.17; N, 8.77. Found: C, 57.53; H, 5.02; N, 8.58.

10

Example 319

(2-Methoxyphenyl)-[2,3-dichloro-4(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl) phenyl] sulfide

The title compound was prepared according to the procedures of Example 310.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.66-1.83 (m, 2H), 1.95-2.09 (m, 2H), 2.57-2.69 (m, 1H), 2.94-3.08 (m, 1), 3.15-3.31 (m, 1H), 3.72 (s, 3H), 3.90-4.05 (m, 1H), 4.41-4.55 (m, 1H), 6.55 (d, J=9Hz, 1H), 6.73 (d, J=15Hz, 1H), 7.00-7.05 (m, 2H), 7.27 (d, J=8Hz, 1H), 7.44-7.50 (m, 2H), 7.92 (d, J=15Hz, 1H). Anal. Calcd. for C<sub>22</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>4</sub>S: C, 56.66; H, 4.54; N, 3.00. Found: C, 56.89; H, 4.84; N, 2.64.

20

Example 320

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(Benzodioxan-6-yl)[2-chloro-4-(E-((4-(tetrazol-5-yl)piperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 314 substituting 3-(tetrazol-5-yl)piperidine with 4-(tetrazol-5-yl)piperidine. The crude  
 5 reaction product was purified by reversed-phase HPLC. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.22 (m, 1H), 1.55-1.75 (m, 2H), 2.06 (m, 1H), 2.45 (m, 1H), 4.22 (m, 4H), 4.30 (m, 4H), 6.70 (m, 1H), 7.00 (dd, J=2.0, 8.0 Hz, 2H), 7.25-7.40 (m, 4H), 7.50 (m, 1H). MS (ESI) m/z 484 (M+H)<sup>+</sup>.

Example 321

(2-Methoxyphenyl)-[3-chloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl]sulfide

The title compound was prepared according to the procedures of Example 1, giving a white solid, m.p. 124-125C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 3.60-3.80 (m, 8H), 3.85 (s, 3H), 6.80 (d, J=15 Hz, 1H), 6.95-7.01 (m, 2H), 7.05 (dd, J=9Hz, 2 Hz,  
 15 1H), 7.15 (d, J=2Hz, 1H), 7.35-7.48 (m, 3H), 7.75 (d, J=15 Hz, 1H). Anal. Calcd. for C<sub>20</sub>H<sub>20</sub>ClNO<sub>3</sub>S: C, 61.61; H, 5.17; N, 3.59. Found: C, 61.43; H, 5.30; N, 3.73.

Example 322

(2-Isopropylphenyl)[2-nitro-4-(E-((4-oxopiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

20

The title compound was prepared according to the procedures of Example 1. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 8.45 (s, 1H), 7.50-7.57 (m, 3H), 7.42(br d, 1H, J = 8.1

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Hz), 7.30 (m, 1H), 7.02 (br, 1H), 6.72 (d, 1H,  $J = 8.4$  Hz), 4.01 (br s, 4H), 3.44 (quintet, 1H,  $J = 6.8$  Hz), 2.56 (br m, 4H), 1.18 (d, 6H,  $J = 7.1$  Hz). MS (ESI)  $m/z$  425, 457. Anal. Calcd for  $C_{23}H_{24}N_2O_4S$ : C, 65.07; H, 5.70; N, 6.60. Found: C, 64.92; H, 5.67; N, 6.62.

5

### Example 323

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-*R*-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 248, substituting ethyl ( $\pm$ )nipecotate with ethyl nipecotate tartrate, giving a white solid.  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  1.26 (t,  $J = 7.4$  Hz, 3H), 1.46-1.67 (m, 1H), 1.67-1.98 (m, 2H), 1.98-2.23 (m, 1H), 2.46-2.63 (m, 1H), 3.10-3.42 (m, 1H), 3.53-4.13 (m, 2H), 4.16 (q,  $J = 7.4$  Hz, 2H), 4.25-4.40 (m, 4H), 4.60-4.88 (m, 1H), 6.91 (d,  $J = 8.4$  Hz, 1H), 6.93 (d,  $J = 15.3$  Hz, 1H), 6.97-7.05 (m, 2H), 7.07 (d,  $J = 2.7$  Hz, 1H), 7.42 (d,  $J = 8.4$  Hz, 1H), 7.59 (d,  $J = 15.3$  Hz, 1H), 7.77 (s, 1H). MS (ESI $^+$ ) ( $M+H$ ) $^+$  at  $m/z$  522.

### Example 324

(Benzodioxan-6-yl)[2-trifluoromethyl-4-(*E*-((3-*R*-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 251, substituting the ethyl ester from Example 248 with ethyl ester from Example 323, giving a white solid.  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  1.48-1.71 (m, 1H), 1.71-2.01 (m,

2H), 2.01-2.20 (m, 1H), 2.53-2.70 (m, 1H), 3.18-3.54 (m, 1H), 3.86-4.20 (m, 2H), 4.20-4.33 (m, 4H), 4.45-4.75 (m, 1H), 6.90 (d,  $J = 8.7$  Hz, 1H), 6.95-7.04 (m, 3H), 7.06 (d,  $J = 2.4$  Hz, 1H), 7.35-7.45 (br m, 1H), 7.60 (d,  $J = 15.3$  Hz, 1H), 7.75 (s, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  494.

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Sub  
A 88Example 325

(Benzodioxan-6-yl)[2,3-dichloro-4-(E-((3-(pyrrolidin-2-on-1-yl)prop-1-ylamino)carbonyl) ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 240,

- 10 substituting 4-fluoro-3-trifluoromethylbenzaldehyde with 2,3-dichloro-4-trifluoromethanesulfoxybenzaldehyde, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.71-1.82 (m, 2H), 2.08 (p,  $J = 7.5$  Hz, 2H), 2.46 (t,  $J = 7.5$  Hz, 2H), 3.2603.50 (m, 6H), 4.23-4.36 (m, 4H), 6.36 (t,  $J = 15.6$  Hz, 1H), 6.60 (d,  $J = 8.7$  Hz, 1H), 6.44 (d,  $J = 8.7$  Hz, 1H), 7.03 (dd,  $J = 2.4, 8.7$  Hz, 1H), 7.09 (d,  $J = 2.4$  Hz, 1H), 15 7.31 (d,  $J = 8.7$  Hz, 1H), 7.94 (d,  $J = 15.6$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  507, 509, 511. Anal. Calcd for C<sub>24</sub>H<sub>24</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>4</sub>S · 1.87 H<sub>2</sub>O: C, 53.27; H, 5.17; N, 5.18. Found: C, 53.30; H, 5.17; N, 4.83.

Example 326

- 20 (Benzodioxan-6-yl)[2,3-dichloro-4-( E-((4-acetylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 325,

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substituting aminopropyl pyrrolidinone with 1-acetylpiperazine. white solid;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.17 (s, 3H), 3.50-3.94 (m, 8H), 4.26-4.40 (m, 4H), 6.61 (d,  $J$  = 8.7 Hz, 1H), 6.71 (d,  $J$  = 15.6 Hz, 1H), 6.95 (d,  $J$  = 8.4 Hz, 1H), 7.04 (dd,  $J$  = 2.4, 8.4 Hz, 1H), 7.09 (d,  $J$  = 2.4 Hz, 1H), 7.30 (d,  $J$  = 8.7 Hz, 1H), 7.99 (d,  $J$  = 15.6 Hz, 1H).

5 MS ( $\text{ESI}^+$ ) ( $\text{M}+\text{Na}^+$ ) at  $m/z$  515, 517, 519. Anal. Calcd for  $\text{C}_{23}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_4\text{S} \cdot 0.52 \text{CH}_2\text{Cl}_2$ : C, 52.55; H, 4.32; N, 5.21. Found: C, 52.63; H, 4.16; N, 4.82.

### Example 327

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((3-carboethoxypiperidin-1-yl)  
10 carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 325, substituting aminopropyl pyrrolidinone with ethyl nipecotate, giving a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.26 (t,  $J$  = 7.0 Hz, 3H), 1.66-1.96 (m, 2H), 1.96-2.21 (m, 1H), 2.44-2.60 (m, 1H), 2.85-3.40 (m, 2H), 3.50-3.70 (m, 1H), 3.80-4.10 (m, 2H),  
15 4.15 (q,  $J$  = 7.0 Hz, 2H), 4.26-4.40 (m, 4H), 6.66 (d,  $J$  = 8.7 Hz, 1H), 6.74 (d,  $J$  = 15.3 Hz, 1H), 6.95 (d,  $J$  = 8.4 Hz, 1H), 7.03 (dd,  $J$  = 2.4, 8.4 Hz, 1H), 7.09 (d,  $J$  = 2.4 Hz, 1H), 7.25-7.38 (m, 1H), 7.93 (d,  $J$  = 15.3 Hz, 1H). MS ( $\text{ESI}^+$ ) ( $\text{M}+\text{Na}^+$ ) at  $m/z$  544, 546, 548.

20

### Example 328

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((4-carboethoxypiperidin-1-yl)  
carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 325, substituting aminopropyl pyrrolidinone with ethyl isonipecotate, giving a white solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.69 (td, *J* = 3.9, 10.8 Hz, 1H), 1.74 (td, *J* = 3.9, 10.8 Hz, 1H), 1.82-2.05 (m, 2H), 2.50-2.63 (m, 1H), 2.84-3.31 (m, 2H), 3.81-4.06 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 4.24-4.34 (m, 4H), 4.34-4.59 (m, 1H), 6.61 (d, *J* = 8.7 Hz, 1H), 6.74 (d, *J* = 15.6 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 7.03 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.08 (d, *J* = 2.7 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 15.6 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 522, 524, 526. Anal. Calcd for C<sub>25</sub>H<sub>25</sub>Cl<sub>2</sub>NO<sub>5</sub>S: C, 57.48; H, 4.82; N, 2.68. Found: C, 57.82; H, 4.96; N, 2.28.

#### Example 329

(Benzodioxan-6-yl)[2,3-dichloro-4-(*E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 155, substituting the ethyl ester from Example 137 with the ethyl ester from Example 327, and KOH with NaOH, providing a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.70-2.0 (m, 2H), 2.0-2.20 (m, 1H), 2.54-2.68 (m, 1H), 3.03-3.46 (m, 2H), 3.80-4.11 (m, 2H), 4.27-4.40 (m, 4H), 4.50-4.70 (m, 1H), 6.60 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 15.3 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 7.03 (dd, *J* = 2.1, 8.5 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 7.93 (d, *J* = 15.3 Hz, 1H). MS (ESI<sup>+</sup>) (M-2H)<sup>+</sup> at *m/z* 492, 494, 496. Anal. Calcd for C<sub>23</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>5</sub>S · 0.73 H<sub>2</sub>O: C, 54.43; H, 4.46; N, 2.76. Found: C, 54.43; H, 4.39; N, 2.49.

Example 330

(Benzodioxan-6-yl)[2,3-dichloro-4-( E-((4-carboxypiperidin-1-yl) carbonyl)ethenyl)  
phenyl] sulfide

5           The title compound was prepared by the procedures described in Example 155,  
substituting the ethyl ester from Example 137 with the ethyl ester from Example 328,  
and KOH with NaOH, to produce a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ  
1.33-1.55 (m, 2H), 1.62-1.78 (m, 2H), 1.93-2.07 (m, 1H), 2.90 (brt, *J* = 10.5 Hz, 1H),  
3.16 (brt, *J* = 10.5 Hz, 1H), 3.96 (br d, *J* = 13.5 Hz, 1H), 4.09 (br d, *J* = 13.5 Hz, 1H),  
10   4.26-4.42 (m, 4H), 6.60 (d, *J* = 9.0 Hz, 1H), 7.04-7.08 (m, 2H), 7.13 (d, *J* = 1.5 Hz,  
1H), 7.22 (d, *J* = 15.3 Hz, 1H), 7.70 (d, *J* = 15.3 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 1H). MS  
(ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 516, 518, 520. Anal. Calcd for C<sub>23</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>1</sub>NaO<sub>5</sub>S · 0.36  
Et<sub>2</sub>O: C, 54.06; H, 4.38; N, 2.58. Found: C, 53.99; H, 4.37; N, 2.22.

Example 331

<sup>15</sup>  
SUB  
A89   (2-Isopropylphenyl)[2,3-dichloro-4-( E-((3-(1-pyrrolidin-2-onyl)propylamino)  
carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 325,  
substituting 6-mercaptobenzodioxane with 2-isopropylbenzenethiol, to give a white  
20   solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.19 (d, *J* = 7.2 Hz, 6H), 1.76 (p, *J* = 5.8 Hz,  
2H), 2.08 (p, *J* = 7.65 Hz, 2H), 2.46 (t, *J* = 7.65 Hz, 2H), 3.32 (q, *J* = 5.8 Hz, 2H),  
3.36-3.51 (m, 5H), 6.35 (d, *J* = 15.3 Hz, 1H), 6.40 (d, *J* = 8.7 Hz, 1H), 7.10 (brt, *J* =

7.5 Hz, 1H), 7.20-7.30 (m, 2H), 7.42-7.53 (m, 2H), 7.94 (d,  $J = 15.3$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  491, 493, 495. Anal. Calcd for C<sub>25</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S · 0.7 CH<sub>2</sub>Cl<sub>2</sub>: C, 56.03; H, 5.38; N, 5.08. Found: C, 56.06; H, 5.22; N, 5.01.

5

Example 332

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-acetylpiperazin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 326, substituting 6-mercaptobenzodioxane with 2-isopropylbenzenethiol, providing a white  
10 solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.19 (d,  $J = 7.2$  Hz, 6H), 2.17 (s, 3H), 3.46 (septet,  $J = 7.2$  Hz, 1H), 3.50-3.90 (m, 8H), 6.41 (d,  $J = 8.7$  Hz, 1H), 6.71 (d,  $J = 15.3$  Hz, 1H), 7.21-7.35 (m, 2H), 7.44-7.57 (m, 3H), 7.99 (d,  $J = 15.3$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  477, 479, 481. Anal. Calcd for C<sub>24</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>S · 0.32 CH<sub>2</sub>Cl<sub>2</sub>: C, 57.89; H, 5.32; N, 5.55. Found: C, 57.85; H, 5.25; N, 5.74.

15

Example 333

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 327, substituting 6-mercaptobenzodioxane with 2-isopropylbenzenethiol, giving a white  
20 solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.20 (d,  $J = 7.2$  Hz, 6H), 1.20-1.35 (m, 5H), 1.65-1.93 (m, 1H), 1.93-2.16 (m, 1H), 2.43-2.58 (m, 1H), 3.06-3.35 (m, 1H), 3.47

(septet,  $J = 7.2$  Hz, 1H), 3.77-4.23 (m, 4H), 4.50-4.77 (m, 1H), 6.41 (d,  $J = 8.4$  Hz, 1H), 6.80 (d,  $J = 15.3$  Hz, 1H), 7.18-7.32 (m, 2H), 7.40-7.55 (m, 2H), 7.93 (d,  $J = 15.3$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  506, 508, 510.

5

Example 334

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 328, substituting 6-mercaptobenzodioxane with 2-isopropylbenzenethiol, to give a white  
10 solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz)  $\delta$  1.19 (d,  $J = 7.2$  Hz, 6H), 1.26 (t,  $J = 7.05$  Hz, 3H), 1.69 (td,  $J = 3.9, 10.8$  Hz, 1H), 1.74 (td,  $J = 3.9, 10.8$  Hz, 1H), 1.88-2.06 (m, 2H), 2.50-2.63 (m, 1H), 2.84-3.08 (m, 1H), 3.08-3.32 (m, 1H), 3.47 (septet,  $J = 7.2$  Hz, 1H), 3.86-4.06 (m, 1H), 4.15 (q,  $J = 7.05$  Hz, 2H), 4.37-4.61 (m, 1H), 6.40 (d,  $J = 8.7$  Hz, 1H), 6.73 (d,  $J = 15.6$  Hz, 1H), 7.22-7.35 (m, 2H), 7.44-7.57 (m, 3H), 7.92 (d, 15  $J = 15.6$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  506, 508, 510. Anal. Calcd for C<sub>26</sub>H<sub>29</sub>Cl<sub>2</sub>NO<sub>3</sub>S · 0.01 H<sub>2</sub>O: C, 61.64; H, 5.77; N, 2.76. Found: C, 61.64; H, 5.90; N, 2.70.

Example 335

20 (2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 329,

0011795-03100

substituting 6-mercaptobenzodioxane with 2-isopropylbenzenethiol, giving a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.19 (d,  $J = 7.2$  Hz, 1H), 1.43-1.67 (m, 1H), 1.67-1.97 (m, 2H), 1.97-2.19 (m, 1H), 2.52-2.64 (m, 1H), 3.04-3.38 (m, 1H), 3.47 (septet,  $J = 7.2$  Hz, 1H), 3.75-4.10 (m, 2H), 4.44-4.70 (m, 1H), 6.40 (d,  $J = 8.4$  Hz, 1H), 6.79 (d,  $J = 15.3$  Hz, 1H), 7.18-7.29 (m, 2H), 7.41-7.53 (m, 3H), 7.93 (d,  $J = 15.3$  Hz, 1H). MS ( $\text{ESI}^+$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  478, 480, 482. Anal. Calcd for  $\text{C}_{24}\text{H}_{25}\text{Cl}_2\text{NO}_3\text{S} \cdot 0.05 \text{H}_2\text{O} \cdot 0.01 \text{EtOH}$ : C, 60.13; H, 5.29; N, 2.92. Found: C, 60.14; H, 5.11; N, 2.52.

10

Example 336

(2-Isopropylphenyl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 330, substituting 6-mercaptobenzodioxane with 2-isopropylbenzenethiol, giving a white solid.  $^1\text{H}$  NMR ( $\text{d}^6\text{-DMSO}$ , 300 MHz)  $\delta$  1.16 (d,  $J = 7.2$  Hz, 6H), 1.33-1.53 (m, 2H), 1.64-1.78 (m, 2H), 1.97-2.10 (m, 1H), 2.88 (brt,  $J = 10.5$  Hz, 1H), 3.15 (brt,  $J = 10.5$  Hz, 1H), 3.97 (br d,  $J = 13.2$  Hz, 1H), 4.11 (br d,  $J = 13.2$  Hz, 1H), 6.41 (d,  $J = 9.0$  Hz, 1H), 7.22 (d,  $J = 15.6$  Hz, 1H), 7.31-7.42 (m, 1H), 7.53 (d,  $J = 7.8$  Hz, 1H), 7.56-7.64 (m, 2H), 7.71 (d,  $J = 15.6$  Hz, 1H), 7.85 (d,  $J = 9.0$  Hz, 1H). MS ( $\text{ESI}^+$ ) ( $\text{M}+\text{H}$ ) $^+$  at  $m/z$  478, 480, 482. Anal. Calcd for  $\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{NNaO}_3\text{S} \cdot 0.95 \text{H}_2\text{O}$ : C, 55.70; H, 5.04; N, 2.71. Found: C, 55.69; H, 4.90; N, 2.57.

Example 337

(1-Methylindol-5-yl)[2,3-dichloro-4-( E-((3-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 283, substituting 4-fluoro-3-chlorobenzaldehyde with 2,3-dichloro-4-trifluoromethanesulfoxybenzaldehyde, giving a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.23 (t, *J* = 7.5 Hz, 3H), 1.46-1.67 (m, 1H), 1.67-1.95 (m, 2H), 1.95-2.17 (m, 1H), 2.43-2.60 (m, 1H), 3.02-3.42 (m, 1H), 3.67-3.92 (m, 2H), 3.86 (s, 3H), 4.13 (q, *J* = 7.5 Hz, 2H), 4.59-4.80 (m, 1H), 6.46 (d, *J* = 8.7 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 6.77 (d, *J* = 15.3 Hz, 1H), 7.15 (d, *J* = 3.0 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.89 (s, 1H), 7.92 (d, *J* = 15.3 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 517, 519, 521.

Example 338

(1-Methylindol-5-yl)[2,3-dichloro-4-( E-((3-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 155, substituting the ethyl ester from Example 137 with ethyl ester from Example 337, and KOH with NaOH, to give a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.29-1.45 (m, 1H), 1.45-1.78 (m, 2H), 1.78-2.02 (m, 1H), 2.20-2.40 (m, 1H), 2.82 (brt, *J* = 10.5 Hz, 1H), 3.08 (brt, *J* = 10.5 Hz, 1H), 3.80-4.07 (m, 2H), 3.86 (s, 3H), 4.38-4.50 (m, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 7.19 (d, *J* = 15.3 Hz, 1H), 7.32

(dd,  $J = 1.8, 8.7$  Hz, 1H), 7.48 (d,  $J = 3.0$  Hz, 1H), 7.64 (d,  $J = 8.7$  Hz, 1H), 7.67-7.77 (m, 2H), 7.87 (d,  $J = 1.8$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  489, 491, 493. Anal. Calcd for C<sub>24</sub>H<sub>22</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S · 0.56 CH<sub>2</sub>Cl<sub>2</sub>: C, 54.94; H, 4.34; N, 5.22. Found: C, 54.89; H, 4.44; N, 5.32.

5

### Example 339

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((4-carboethoxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

The title compound was prepared by the procedures described in Example 285, substituting 4-fluoro-3-chlorobenzaldehyde with 2,3-dichloro-4-trifluoromethanesulfoxybenzaldehyde, providing a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.25 (t,  $J = 7.2$  Hz, 3H), 1.62-1.79 (m, 2H), 1.87-2.04 (m, 2H), 2.41-2.63 (m, 1H), 2.85-3.41 (m, 2H), 3.85 (s, 3H), 3.87-4.10 (m, 1H), 4.15 (q,  $J = 7.2$  Hz, 2H), 4.32-4.60 (m, 1H), 6.46 (d,  $J = 8.7$  Hz, 1H), 6.54 (d,  $J = 3.0$  Hz, 1H), 6.71 (d,  $J = 15.3$  Hz, 1H), 7.15 (d,  $J = 3.0$  Hz, 1H), 7.17 (d,  $J = 8.7$  Hz, 1H), 7.36 (dd,  $J = 2.4, 8.4$  Hz, 1H), 7.42 (d,  $J = 8.4$  Hz, 1H), 7.88 (d,  $J = 2.4$  Hz, 1H), 7.90 (d,  $J = 15.3$  Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at  $m/z$  517, 519, 521. Anal. Calcd for C<sub>26</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>3</sub>S · 0.12 H<sub>2</sub>O: C, 60.10; H, 5.09; N, 5.39. Found: C, 60.09; H, 5.21; N, 5.54.

20

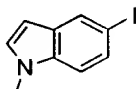
### Example 340

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl) phenyl] sulfide

00750 55/74560

The title compound was prepared by the procedures described in Example 155, substituting the ethyl ester from Example 137 with ethyl ester from Example 339, and KOH with NaOH, to give a white solid. <sup>1</sup>H NMR (d<sup>6</sup>-DMSO, 300 MHz) δ 1.31-1.53 (m, 2H), 1.62-1.76 (m, 2H), 1.94-2.09 (m, 1H), 2.88 (brt, *J* = 10.5 Hz, 1H), 3.13 (brt, *J* = 10.5 Hz, 1H), 3.86 (s, 3H), 3.93 (br d, *J* = 13.2 Hz, 1H), 4.09 (br d, *J* = 13.2 Hz, 1H), 6.41 (d, *J* = 8.7 Hz, 1H), 6.53 (dd, *J* = 0.9, 3.0 Hz, 1H), 7.04 (d, *J* = 15.3 Hz, 1H), 7.32 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.48 (d, *J* = 3.0 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 15.3 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.88 (d, *J* = 2.1 Hz, 1H). MS (ESI<sup>+</sup>) (M+H)<sup>+</sup> at *m/z* 489, 491, 493. Anal. Calcd for C<sub>24</sub>H<sub>21</sub>Cl<sub>2</sub>N<sub>2</sub>NaO<sub>3</sub>S · 0 H<sub>2</sub>O: C, 56.37; H, 4.14; N, 5.48. Found: C, 56.44; H, 4.38; N, 5.20.

An alternative method for preparing Example 340 is given below.

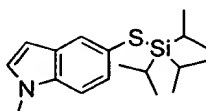


Example 340A

1-Methyl-5-iodoindole

Sub A90  
15 To a solution of 5-iodoindole (75 g, 0.31 mol) in dry THF (750mL), at -78°C was added sodium hydride (60% in mineral oil, 14.85 g, 0.37 mol) in one portion. The suspension was stirred at -78°C for 1 hour after which iodomethane (28.8 mL, 0.46 mol) was added. The reaction mixture was stirred overnight with a slow elevation on temperature to room temperature (no more dry ice was added). Ether (600mL) and hexane (1.2L) were added and the mixture was washed with brine (1.6L) and water (1.5L), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The solution was concentrated and the residual brown solid was recrystallized from hexane to give the title compound

Sub  
A90  
(66 g). The impure fraction from the mother liquor was flash chromatographed (8% EtOAc in hexane) to give an additional quantity of desired product (12.5 g, combined yield of 99%). MS (DCI/NH<sub>3</sub>) m/e 258 (M+H)<sup>+</sup>.



5

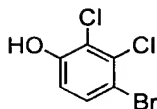
Example 340B1-Methyl-S-triisopropylsilyl-5-indolethiol

Sub  
A9  
Potassium hydride (35% in mineral oil, 12.03 g, 0.105 mol) was charged to a 250 mL RBF and was washed with dry THF (2x50mL). The resultant KH powder was then suspended in dry THF (75 mL), and cooled to 5 °C. Triisopropylsilylthiol (20.0 g, 0.105 mol) was slowly added via syringe over a period of 15 minutes.

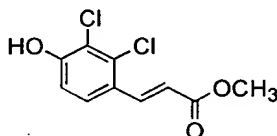
Vigorous escape of hydrogen gas was observed with addition of the thiol. The suspension was stirred at 5°C for 1 our and became homogenous. After another hour stirring at room temperature, this solution was cannulated to a THF solution (100mL)

15 containing Example 340A (24.5 g, 95.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (2.2 g, 1.91 mmol). The yellow suspension was stirred at 70°C for 1 hour. After cooled, ether and hexane were added, and the mixture was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The residual oil was purified by flash chromatography (silica gel, 3% EtOAc in hexane) to give the  
20 title compound (26.7 g, 88%). MS (DCI/NH<sub>3</sub>) m/e 320 (M+H)<sup>+</sup>.

290

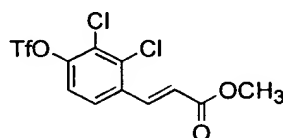
Example 340C4-Bromo-2,3-dichlorophenol

To a solution of 2,3-dichlorophenol (200 g, 1.227 mol) in dichloromethane (800 mL), at 0 °C was added dropwise bromine (196.1g, 1.227 mol) from a dropping funnel within 1 hour. The red solution was stirred overnight (0°C - rt), and washed with 10% NaHSO<sub>3</sub>. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residual white solid was recrystallized from hexane to give example 340C as white needles (207g, 70%). MS (DCI/NH<sub>3</sub>) *m/e* 241 (M+H)<sup>+</sup>.

Example 340DMethyl 2,3-dichloro-4-(4-hydroxyphenyl)acrylate

A 1 L RBF was charged with Example 340C (48.4 g, 0.2 mol), Pd<sub>2</sub>(dba)<sub>3</sub> (4.6 g, 5 mmol), (Tol)<sub>3</sub>P (4.66 g, 15.2 mmol), and purged with nitrogen. Dry DMF (300 mL), methyl acrylate (51.66 g, 0.6 mol) and triethylamine (84 mL, 0.6 mol) were then added. The reaction mixture was purged with nitrogen and stirred at 100°C (oil bath) for 16 hours. After cooled to room temperature, a lot of white crystalline material formed. Ethyl acetate (500 mL) and brine (not saturated, 800 mL) were added, and stirred. The white crystalline material dissolved. A little insoluble black solid (Pd)

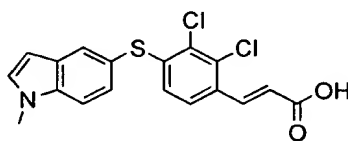
Sub  
A92  
was filtered off. To the solution was then added, with stirring, saturated NaCl solution (2 L) and hexane (500 mL). The mixture was stirred for 1 hour. The formed yellowish solid was collected by filtration, washed with water (400 mL), acetonitrile (50 mL) and 1:1 ethyl acetate/hexane (500 mL), and dried to give pure desired compound (44.99g, 91%). MS (DCI/NH<sub>3</sub>) *m/e* 247 (M+H)<sup>+</sup>.



#### Example 340E

##### Methyl 2,3-dichloro-4-(trifluoromethane sulfonyloxyphenyl)acrylate

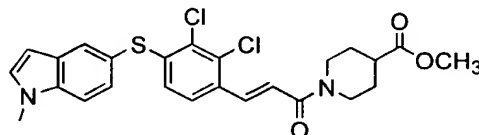
10 To a suspension of Example 340D (18.62 g, 75.4 mmol) in pyridine (150 mL) at 5°C was added trifluoromethylsulfonyl anhydride (25.53 g, 90 mmol) very slowly. The suspension was stirred at 5 °C for 1 hour and became homogeneous. The solution was kept at 5 °C for 2 hours and at room temperature for 20 minutes. Ether (700mL) was added and the mixture was washed 10%HCl (700 mL)/brine (300 mL), 10%HCl  
15 (100 mL)/brine (900 mL), and brine (500 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give the title compound (24.86 g, 87%). MS (DCI/NH<sub>3</sub>) *m/e* 379 (M+H)<sup>+</sup>.



Example 340F(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-(carboxyethenyl)phenyl] sulfide

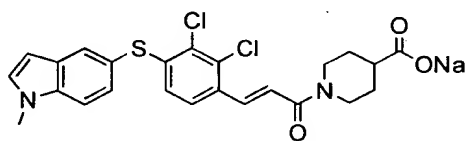
To a solution of Example 340B (38.5 g, 0.12 mol) and Example 340E (30.3 g, 0.08 mol) in dry N-methylpyrrolidinone (300 mL) was added CsF (18.2 g, 0.12 mol) at 5°C under nitrogen atmosphere. After 1 hour stirring at the same temperature, the cooling bath was removed, and the mixture was stirred at room temperature for 0.5 hour. Ethyl acetate (800 mL) was added, and the mixture was washed with brine and water, and concentrated. The residual oil was separated by flash chromatography (20% EtOAc/hexane) to give a yellow solid (30 g).

This yellow solid was dissolved in THF (150 mL), and was added a solution of LiOH (4.0 g, 0.16 mol) in H<sub>2</sub>O (50 mL). The mixture was stirred at room temperature for 1 hour and more water (100 mL) was added to form a transparent solution. After overnight stirring the solution was acidified with 10 % aq. HCl. The mixture was concentrated under reduced pressure to about 100 mL. The formed solid material was collected by filtration, washed with water (200 mL), acetonitrile (30 mL), 1:1 ether/hexane, and dried to give the title compound (22.3 g, overall 74%). MS (DCI/NH<sub>3</sub>) *m/e* 378 (M+H)<sup>+</sup>.

Example 340G

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((4-carbomethoxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

To a solution of Example 340F (9.5 g, 25.1 mmol) and methyl isonipecotate (7.19 g, 50.2 mmol) in DMF (70 mL) was added EDC (9.64 g, 50.2 mmol), HOBT (6.78 g, 50.2 mmol) and triethylamine (7.0 mL, 50.2 mmol). The reaction mixture was stirred at room temperature for 15 hours. Ethyl acetate (800 mL) was added, and the mixture was washed with brine, and concentrated. The residue was purified by flash chromatography (60% EtOAc in hexane) to give example 340G as white powder (10.86 g, 94%). MS (ESI<sup>+</sup>) *m/z* 503 (M+H)<sup>+</sup>.



Example 340

(1-Methylindol-5-yl)[2,3-dichloro-4-(*E*-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide, sodium salt

To a suspension of Example 340G (11.8 g, 23.6 mmol) in THF (150 mL) was added a solution of lithium hydroxide monohydrate (1.98 g, 47.2 mmol) in H<sub>2</sub>O (30 mL). The mixture was stirred at room temperature overnight. Water (120 mL) was added and formed transparent solution was stirred for another hour before 10% HCl (30 mL) was added. The mixture was concentrated under reduced pressure to about 120 mL. The formed solid material was collected by filtration, washed with water, acetonitrile, and dried to give a white solid (11.0 g).

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A93

10.50 grams of the solid was suspended in methanol (60 mL), and was treated with a solution NaOH (0.859g) in methanol (20 mL). After all of the solid material went into solution, the solvent was removed under reduced pressure. The residual yellow oil was triturated with ether, and dried to give the title compound as yellow powder (11.33 g, 95%).

#### Example 341

(2-Ethoxyphenyl)-[2,3-dichloro-4(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

10 The title compound was prepared according to the procedures of Example 310, substituting 2-ethoxybenzenethiol prepared according to the procedures of Example 97A. <sup>1</sup>H-NMR (CD<sub>3</sub>OD, 300 MHz) Potassium salt δ 1.20 (t, J=7Hz, 3H), 1.55-1.72 (m, 2H), 1.88-1.98 (m, 2H), 2.32 (m, 1H), 2.88 (t, J=12Hz, 1H), 3.20 (t, J=12 Hz, 1H), 4.05 (q, J=7Hz, 2H), 4.14 (d, J=12 Hz, 1H), 4.48, (d, J= 12 Hz, 1H), 6.64 9d, J=9Hz, 1H), 7.00-7.15 (m, 3H), 7.44-7.50 (m, 2H), 7.56 (d, J=9Hz, 1H), 7.90 (d, J=15 Hz, 1H) Anal. Calcd. for C<sub>23</sub>H<sub>22</sub>KCl<sub>2</sub>NO<sub>4</sub>S 0.5 H<sub>2</sub>O: C, 52.37, H, 4.39, N, 2.66. Found: C, 52.23; H, 4.56; N, 2.49.

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A94

#### Example 342

20 (2-Ethoxyphenyl)-[2,3-dichloro-4(E-[(morpholin-1-yl)carbonyl]ethenyl)phenyl] sulfide

The title compound was prepared according to the procedures of Example 310,

substituting 2-ethoxybenzenethiol prepared according to the procedures of Example 97A. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 1.25 (t, J=7Hz, 3H), 3.55-3.80 (m, 8H), 4.05 (q, J=7Hz, 2H), 6.63 (d, J=9Hz, 1H), 6.71 (d, J=15 Hz, 1H), 6.95-7.03 (m, 2H), 7.26 (d, J=9Hz, 1H), 7.39-7.50 (m, 2H), 7.99 (d, J=15 Hz, 1H) Anal. Calcd. for C<sub>21</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>3</sub>S: C, 57.54; H, 4.82; N, 3.20. Found: C, 57.55; H, 4.77; N, 3.14.

### Example 343

(2-Ethoxyphenyl)-[2,3-dichloro-4(E-[(3-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

10 The title compound was prepared according to the procedures of Example 310, substituting 2-ethoxybenzenethiol prepared according to the procedures of Example 97A. <sup>1</sup>H-NMR (CD<sub>3</sub>OD 300MHz) δ 1.20 (t, J=7Hz, 3H), broad peaks totaling 9 protons at 1.4-1.95, 2.0-2.14, 2.22-2.35, 2.75-3.13, 4.10-4.34, 4.69-4.76, 4.05 (q, J=7Hz, 2H), 6.64 (d, J=9Hz, 1H), 7.03 (t, J=8Hz, 1H), 7.10 (d, J=9Hz, 1H), 7.22 (d, J=15 Hz, 1H), 7.45-7.50 (m, 2H), 7.62 (d, J=9Hz, 1H), 7.80 (d, J=15 Hz, 1H). The acid (303 mg, 0.63 mmol) was dissolved in 3 mL of methanol. A solution of KOH (0.60 mmol) in 1 mL of methanol was added. The resultant solution was stirred for 5 min and concentrated in vacuo. Ether (5 mL) was added, and the mixture was stirred for 1 hr. The resultant powder was collected by filtration and dried under vacuum at 20 60C to give 307 mg of a solid, water-soluble product. Anal. Calcd. for C<sub>23</sub>H<sub>22</sub>KC<sub>12</sub>NO<sub>4</sub>S 0.5 H<sub>2</sub>O; C, 52.37; H, 4.39; N, 2.66. Found: C, 52.20; H, 4.65, N, 3.04.

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Example 344

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carboethoxypyrrolidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

- 5        Prepared according to the procedures of Example 71, giving a yellow solid.
- <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 7.0 Hz, 6H); 1.20 (t, J= 7.0 Hz, 3H); 1.92-2.30 ( m, 2H); 3.10-4.01 (m, 6H); 4.06-4.17 (m, 2H); 6.64 (d, J = 8.5 Hz, 1H); 7.06-7.17 (m, 1H), 7.34-7.62 (m, 5H); 7.88-7.96 (m, 1H); 8.62 (dd, J = 1.5, 8.5 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 469. Anal calcd for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>S<sub>1</sub>O<sub>5</sub>: C, 64.08; H, 6.02; N, 5.98. Found: C, 64.12; H, 5.98; N, 5.89.
- 10

Example 345

(2-Isopropylphenyl)[2-nitro-4-( E-((3-carboxypyrrolidin-1-yl)carbonyl)ethenyl)  
phenyl] sulfide

- 15        Prepared according to the procedures of Example 71, giving a yellow solid.
- <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.14 (d, J = 6.8 Hz, 6H); 1.92-2.24 ( m, 2H); 3.01-3.92 (m, 6H); 6.64 (dd, J = 1.7, 8.5 Hz, 1H); 7.04-7.16 (m, 1H), 7.33-7.61 (m, 5H); 7.87-7.95 (m, 1H); 8.61 (dd, J = 1.7, 8.5 Hz, 1H). MS (APCI) (M+H)<sup>+</sup> at m/z 441. Anal calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>S<sub>1</sub>O<sub>5</sub>: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.47; H, 5.39; N, 6.09.
- 20

Example 346

(2-Isopropylphenyl)[2,3-difluoro-4-( E-((3-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.18 (d, J = 7.0 Hz, 6H); 1.10-1.22 (m, 3H); 1.30-2.07 (br m, 4H); 2.50-3.45 (br m, 3H); 3.55-4.47 (br m, 5H); 6.62-6.72 (m, 1H); 7.23-7.73 (m, 7H). MS (APCI) (M+H)<sup>+</sup> at m/z 474.

Example 347

(2-Isopropylphenyl)[2,3-difluoro-4-( E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.18 (d, J = 7.0 Hz, 6H); 1.30-2.03 (br m, 4H); 2.25-3.50 (br m, 4H); 3.87-4.51 (br m, 2H); 6.62-6.72 (m, 1H); 7.23-7.73 (m, 7H). MS (APCI) (M+H)<sup>+</sup> at m/z 446.

Example 348

(2-Isopropylphenyl)[2,3-difluoro-4-( E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 71, giving a yellow solid.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300MHz) δ 1.18 (d, J = 6.8Hz, 6H); 1.30-1.91 (br m, 4H); 2.50-3.50 (br m, 4H); 4.02-4.34 (br m, 2H); 6.62-6.72 (m, 1H); 7.23-7.73 (m, 7H). MS (APCI) (M+H)<sup>+</sup> at m/z 446.



(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-( E-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Example 351A

5 3-Chloro-4-hydroxy-2-(trifluoromethyl)benzaldehyde

Chloroform (6.7g, 2.0 eq.) was added dropwise to a stirred mixture of Ca(OH)<sub>2</sub> (8.95g, 120 mmol.), K<sub>2</sub>CO<sub>3</sub> (13.5g, 98 mmol.), 2-chloro-3-(trifluoromethyl)phenol (5.0g, 22 mmol.), and H<sub>2</sub>O (50 mL) at 60°-70° over 2 h. The reaction mixture was cooled, and acidified with conc. HCl. The product was extracted into EtOAc and dried  
10 over Na<sub>2</sub>SO<sub>4</sub>. Solvent was evaporated, the crude product was separated and purified through a silica column, eluting with hexane and EtOAc (3:2) to give 580 mg (10%) of the title compound.

Example 351B

15 (2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-( E-carboxyethenyl) phenyl] sulfide

The title compound was prepared according to the procedures described in Example 310, substituting the compound of Example 351A for 4-hydroxy-2,3-dichlorobenzaldehyde.

20 Example 351C

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-( E-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

To the acyl chloride (37 mg, 0.1 mmol) prepared from the compound of Example 351B, as a solution in  $\text{CH}_2\text{Cl}_2$  was added 1.2 eq. of ethyl isonipecotate and 1.2 eq. of Hunig's base. The mixture was stirred at room temperature for 20 min., ~90% of the solvent was removed in vacuo, and the resultant solution was loaded on a silica column to elute with hexane and EtOAc (3:2) to give 51mg (98%) of the title compound.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ , 300MHz)  $\delta$  1.25 (t,  $J=7.5\text{Hz}$ , 3H), 1.65-1.78 (m, 2H), 1.92-2.02 (br, 2H), 2.51-2.60 (m, 1H), 2.93-3.24 (br, 2H), 3.82 (s, 3H), 3.88-3.96 (m, 1H), 4.15 (q,  $J=7.5\text{Hz}$ , 2H), 4.40-4.50 (br, 1H), 6.48 (d,  $J=15\text{Hz}$ , 1H), 6.72 (d,  $J=9\text{Hz}$ , 1H), 7.02 (d,  $J=7.5\text{Hz}$ , 2H), 7.12 (d,  $J=9\text{Hz}$ , 1H), 7.49 (t,  $J=9\text{Hz}$ , 2H), 7.86 (qq,  $J=4.5\text{Hz}$ , 1H). MS ( $\text{DCI}/\text{NH}_3$ )  $m/e$  528 ( $\text{M}+\text{H}$ ) $^+$ .

#### Example 352

(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((4-carboethoxypiperidin-1-yl)carbonyl)ethenyl) phenyl] sulfide

The compound of Example 351 was hydrolyzed by aq. NaOH in EtOH at rt. to give 90% yield of the title compound.  $^1\text{H}$  NMR(DMSO, 300MHz)  $\delta$  1.37-1.52 (br. 2H), 1.78-1.86 (br. 2H), 2.45-2.55 (m, 1H), 2.83 (t,  $J=12\text{Hz}$ , 1H), 3.17 (t,  $J=13.5\text{ Hz}$ , 1H), 3.80 (s, 3H), 4.07 (d,  $J=12\text{Hz}$ , 1H), 4.26 (d,  $J=13.5\text{Hz}$ , 1H), 6.75 (d,  $J=9\text{Hz}$ , 1H), 6.98 (d,  $J=15\text{Hz}$ , 1H), 7.11(t,  $J=9\text{Hz}$ , 1H), 7.26 (d,  $J=9\text{Hz}$ , 1H), 7.53 (d,  $J=7.5\text{Hz}$ , 1H), 7.62 (d,  $J=9\text{Hz}$ , 2H), 7.70 (qq,  $J=4.5\text{Hz}$ , 1H). MS ( $\text{DCI}/\text{NH}_3$ )  $m/e$  500( $\text{M}+\text{H}$ ) $^+$ .

Example 353

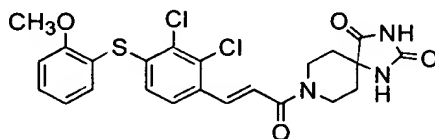
(2-Methoxyphenyl)[2-chloro-3-trifluoromethyl-4-(*E*-((morpholin-1-yl)carbonyl)ethenyl) phenyl] sulfide

Prepared according to the procedures of Example 351, giving 50 mg (91%) of the title compound. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300MHz) δ 3.56-3.62 (br m, 2H), 3.67-3.77 (br m, 6H), 3.85 (s, 3H), 6.45 (d, J=15Hz, 1H), 6.73 (d, J=9Hz, 1H), 7.03 (d, J=9Hz, 2H), 7.09 (t, J=9Hz, 1H), 7.52 (d, J=9Hz, 2H), 2.93 (qq, J=6Hz, 1H). MS (DCI/NH<sub>3</sub>) *m/z* 458 (M+H)<sup>+</sup>.

Example 354

(Benzodioxan-6-yl) [ 4-(*E*-((4-carboxypiperidin-1-yl) carbonyl)ethenyl)naphthyl] sulfide

The methods of Example 310 and 311 were used to convert 4-hydroxy-2-naphthaldehyde and 6-benzodioxanethiol to the desired product as a yellow solid. <sup>1</sup>H NMR (DMS-d<sub>6</sub>, 300MHz) δ 1.50 (br s, 2H), 1.83-1.92 (m, 2H), 2.5-2.6 (m, 1H), 2.85-2.95 (m, 1H), 3.18-3.29 (m, 1H), 4.22 (br s, 5H), 4.30-4.38 (m, 1H), 6.87-6.92 (m, 3H), 7.38 (d, J=15Hz, 1H), 7.45 (d, J=7.5Hz, 1H), 7.64-7.70 (m, 2H), 7.93 (d, J=7.5Hz, 1H), 8.20-8.45 (m, J=3H). MS( ESI<sup>+</sup> ) *m/z* 476 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>25</sub>NO<sub>5</sub>S·0.67H<sub>2</sub>O: C, 66.50; H, 5.44; N, 2.87. Found: C, 66.56; H, 5.81; N, 2.49.

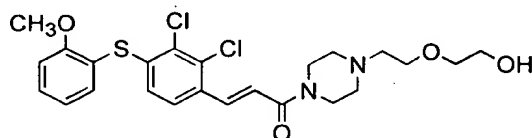


Example 355

(2-Methoxyphenyl) [2,3-dichloro-4-( E-((4-(spiro-hydantoin-5-yl)-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

900  
97

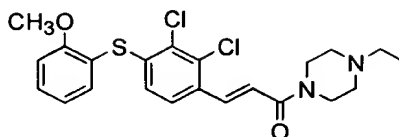
The title compound was prepared from Example 310C, using the procedures described in Example 340 and substituting methyl isonipecotate with piperadine-4-spiro-5'-hydantoin, which was prepared according to a literature method (Wysong, C., et al, *J. Org. Chem.* **1996**, 7650). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.65 (m, 2H), 1.75 (m, 2H), 3.05 (m, 1H), 3.50 (m, 1H), 4.12 (m, 1H), 4.20 (m, 1H), 6.56 (d, J=6.5Hz, 1H), 7.10 (t, J=8.0Hz, 1H), 7.22 (d, J=8.0 Hz, 1H), 7.28 (d, J=15.6 Hz, 1H), 7.49 (dd, J=8.0, 1.7Hz, 1H), 7.56 (t, J=8.2Hz, 1H), 7.76 (d, J=15.6Hz, 1H), 7.84(d, J=8.6Hz, 1H), 8.58 (s, 1H), 10.73(s, 1H). MS (ESI) m/z 504 (M-H)<sup>-</sup>.

Example 356

(2-Methoxyphenyl) [2,3-dichloro-4-( E-(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared from Example 310C by the procedures described in Example 340 and substituting methyl isonipecotate with N-[2-(2-hydroxyethoxy)ethyl]piperazine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 3.10 (m, 2H), 3.50 (m, 4H), 4.50 (m, 2H), 4.70 (s, 1H), 6.57 (d, J=8.5Hz, 1H), 7.09 (t, J=8.0Hz, 1H), 7.23 (d, J=8.0Hz, 1H), 7.26 (d, J=15.5Hz, 1H), 7.49 (dd, J=7.8, 1.7Hz, 1H), 7.57 (t,

J=8.2Hz, 1H), 7.78 (d, J=15.6Hz, 1H), 7.80 (d, J=7.8Hz, 1H). MS (ESI<sup>-</sup>) *m/z* 545 (M-H)<sup>-</sup>.



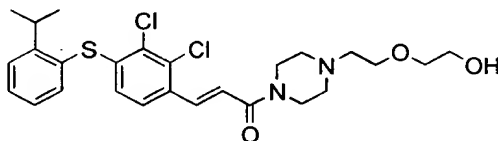
5

### Example 357

(2-Methoxyphenyl)[2,3-dichloro-4-(E-((4-ethylpiperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared from Example 310C by the procedures described in Example 340 and substituting methyl isonipecotate with 1-

10 ethylpiperazine. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.09 (t, J=7.1Hz, 3H), 2.42 (q, J=7.1Hz, 2H), 2.47 (m, 4H), 3.60 (m, 2H), 3.75 (m, 2H), 3.82 (s, 3H), 6.56 (d, J=8.5Hz, 1H), 6.74(d, J=15.3Hz, 1H), 7.02 (m, 2H), 7.26 (d, J=8.5Hz, 1H), 7.46 (m, 2H), 7.94 (d, J=15.5Hz, 1H). MS (ESI<sup>+</sup>) *m/z* 451 (M+H)<sup>+</sup>.



15

### Example 358

(2-Isopropylphenyl)[2,3-dichloro-4-(E-((4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared from the cinnamide acid of Example 331, using the procedures described in Example 340 and substituting methyl isonipecotate with N-[2-(2-hydroxyethoxy)ethyl]piperazine.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.18 (d, 6H), 3.0 (m, 3H), 3.30 (m, 2H), 3.50 (m, 10H), 3.80 (m, 2H), 4.50 (t, 1H), 6.45 (d, 1H), 7.30 (d, 1H), 7.35 (dd, 1H), 7.55 (d, 1H), 7.60 (m, 2H), 7.75 (d, 1H), 7.80 (d, 1H). MS (ESI $^+$ )  $m/z$  523 (M+H) $^+$ .

#### Example 359

(Benzodioxan-6yl)[2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

10

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#### Example 359A

1-Methyl-2,3-bis(trifluoromethyl)-7-oxabicyclo[2.2.1]hepta-2,5-diene

Hexafluoro-2-butyne (21.0 g, 0.13 mol) was transferred into a reaction bottle and added 2-methylfuran (12.86 g, 0.157 mol). This resulting mixture bottle was sealed and heated for 15 hr. at 120 °C. After cooling, the excess 2-methylfuran was rotoevaporated in vacuo at rt, to give crude title product (29 g, 92%), which was used directly.

20

#### Example 359B

4-Methyl-2,3-bis(trifluoromethyl)phenol

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A mixture of Example 359A (12.0 g, 0.05 mol) and boron trifluoride-diethyl ether complex (150 ml) was stirred at room temp overnight, then neutralized carefully with 20% aqueous potassium carbonate, then the mixture was extracted with ether. The ether layer was dried over  $\text{MgSO}_4$  and evaporated under reduced pressure to afford 10.4g (85%) of the title compound.

#### Example 359C

##### 4-[4-Bromobenzene sulfonyloxy-2,3-bis(trifluoromethyl)]benzylbromide

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The phenol compound of Example 359B (10 g, 0.04 mol) was treated with 4-bromobenzenesulfonyl chloride (11.0 g, 0.043 mol) and Hunig's base (5.56 g, 0.043 mol) in  $\text{CH}_2\text{Cl}_2$  (150 ml). The solution was washed with water, brine and dried over  $\text{MgSO}_4$ . After evaporating the solvent, N-bromosuccinimide (7.3 g, 0.04 mol) and benzoyl peroxide (200 mg) were added and the mixture was suspended in  $\text{CCl}_4$  (100ml). The resulting mixture was refluxed for 13 hr. When the reaction was cooled, the white solid was filtered and washed with  $\text{CCl}_4$  to afford the crude title compound. This crude product was used for next step without further purification.

#### Example 359D

##### 4-Hydroxy-2,3-bis(trifluoromethyl)benzaldehyde

20 The crude product of Example 359C was dissolved in 60 ml of DMSO and 20 ml of  $\text{CH}_2\text{Cl}_2$ , and 12 g of trimethylamine N-oxide added. The resulting mixture was stirred at rt for 2.5 hr. The reaction mixture was poured into an ice cold 50% saturated

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5 aqueous NaCl solution (200 ml) and extracted with ether (3X100 ml). The combined organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of solvent, the product was purified by column chromatography, eluted with hexane:EtOAc (3:2) to provide 3.0 g of the title compound, plus 4.0 g of recovered 4-[4-bromobenzenesulfonyloxy-2,3-bis(trifluoromethyl)]toluene.

#### Example 359E

(Benzodioxan-6-yl)-[2,3-bis(trifluoromethyl)-4-(E-carboethenyl)phenyl]sulfide

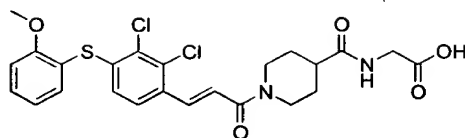
10 The title compound was prepared according to the procedures described in Example 330, substituting the compound of Example 359D for 4-hydrox-2,3-dichlorobenzaldehyde.

#### Example 359F

(Benzodioxan-6yl)[2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

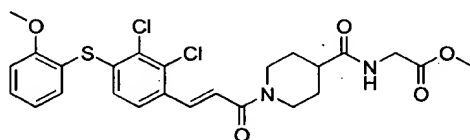
15 The title compound was prepared from Example 359E by the procedures described in Example 330, giving a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300MHz) δ 1.65(br s, 2H), 1.93-2.04 (m, 2H), 2.57-2.65 (m, 1H), 2.95-3.05 (m, 1H), 3.25 (m, 1H), 4.12 (m, 1H), 4.28 (m, 4H), 4.41 (m, 1H), 6.92-7.03 (m, 4H), 7.25 (d, J=9Hz, 1H),  
20 7.72 (d, J=9Hz, 1H), 7.72-7.81 (m, 1H). MS (ESI) *m/e* 562 (M+H)<sup>+</sup>. Anal calcd for C<sub>25</sub>H<sub>21</sub>NO<sub>5</sub>F<sub>6</sub>S: C, 53.48; H, 3.77; N, 2.49. Found: C, 53.42; H, 3.69; N, 2.25.

307

Example 360

(2-Methoxyphenyl) [2,3-dichloro-4-(E-((4-(carboxymethylamino)carbonyl-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

5

Example 360A

(2-Methoxyphenyl)[2,3-dichloro-4-(E-((4-(methylaminomethylcarboxylate)carbonyl-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

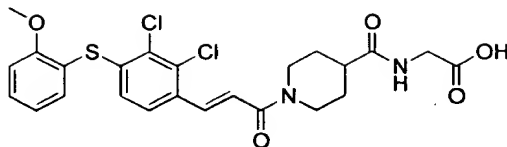
10

The title compound was prepared by the procedure described in Example 363 using glycine methyl ester as the coupling substrate. HPLC (Supelco C-18 column, water:acetonitrile 50:90- 90:50, 9 minute elution, flow rate 1.5 mL/min, rt = 6.11 min. MS (APCI) m/e 537 (M+H)<sup>+</sup>;

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.46(m, 3H), 1.78(br d, 2H), 2.79(m, 1H), 3.15(m, 1H), 3.62(s, 3H), 3.80(s, 3H), 3.83(d, 2H), 4.20(m, 1H), 4.40(m, 1H), 6.58(d, 1H), 7.09(t, 1H), 7.22(d, 1H), 7.25(dd, 1H), 7.48(d, 1H), 7.56(t, 1H), 7.72(d, 1H), 7.81(d, 1H), 8.28(t, 1H). Anal calcd for C<sub>25</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>5</sub>S 1.3 H<sub>2</sub>O: C, 53.54; H, 5.14; N, 4.99. Found: C, 53.49; H, 4.88; N, 4.75.

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Example 360B

(2-Methoxyphenyl) [2,3-dichloro-4-(E-((4-(carboxymethylamino)carbonyl-piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

- 5 The title compound was hydrolyzed as described in Example 340H. HPLC (Supelco C-18 column, water:acetonitrile 90:0- 0:90, 30 minute elution, flow rate 0.8 mL/min) rt 26.14 min. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.46 (m, 2H), 1.75 (m, 2H), 2.73 (m, 1H), 3.12 (m, 1H), 3.70 (m, 2H), 3.79 (s, 3H), 4.02 (m, 1H), 4.20 (m, 1H), 4.41 (m, 1H), 6.65 (d, 1H), 7.09 (dt, 1H), 7.22 (d, 1H), 7.25 (dd, 1H), 7.48 (dd, 1H), 7.58 (m, 1H), 7.72 (d, 1H), 7.82 (d, 1H), 8.11 (m, 1H). MS (APCI) *m/e* 523 (M+H)<sup>+</sup>.

Example 361

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-carboxymethylpiperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

- 15 The title compound was prepared according to the procedures of Example 22, employing the compound of Example 359D as starting material, to give a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz) δ 3.07-3.12 (m, 4H), 3.48 (s, 2H), 3.74 (s, 3H), 3.89 (br s, 4H), 6.99-7.18 (m, 4H), 7.53 (d, J=9Hz, 2H), 7.72 (d, J=9Hz, 1H), 7.78-7.88 (m, 1H). MS (ESI) *m/z* 549 (M+H)<sup>+</sup>. Anal calcd for C<sub>26</sub>H<sub>26</sub>F<sub>6</sub>N<sub>2</sub>O<sub>4</sub>S·0.9HAc: C, 51.43, H, 4.28, N, 4.65. Found: C, 51.48, H, 4.12, N, 4.45.

Example 362

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-N-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 356,  
5 employing the compound of Example 359D as starting material to give an oil. <sup>1</sup>H  
NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.68 (br s, 6H), 3.71 (br s, 4H), 3.80 (br s, 5H), 6.55 (d,  
J=15Hz, 1H), 6.93-7.02 (m, 2H), 7.10 (d, J=9Hz, 1H), 7.35 (d, J=9Hz, 1H), 7.41-7.50  
(m, 2H), 7.82 (qq, J=15Hz, 1H). MS (ESI) *m/z* 535 (M+H)<sup>+</sup>. Anal calcd for  
C<sub>24</sub>H<sub>24</sub>F<sub>6</sub>N<sub>2</sub>O<sub>3</sub>SHCl: C, 50.49; H, 4.41; N, 4.91. Found: C, 50.72; H, 4.70; N, 4.55.

10

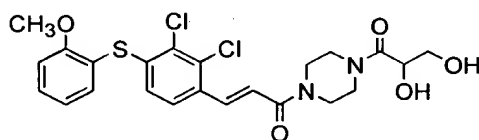
Example 363

(1-Methylindol-5-yl) [2,3-dichloro-4-(E-((4-(carbo-2,3-dihydroxypropylamino)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

To a solution of Example 340H (100mg, 0.2 mmol) and 3-amino-1,2-  
15 propanediol (37.4 mg, 0.41 mmol) in DMF (3 mL) was added EDC (78 mg, 0.41  
mmol), HOBt (55 mg, 0.41 mmol) and triethylamine (0.057 mL, 0.41 mmol). The  
reaction mixture was stirred at room temperature for 15 hours. Ethyl acetate (60 mL)  
was added, and the mixture was washed with brine. The aqueous phase was extracted  
with 10% MeOH in methylene chloride. The combined organic phases were  
20 concentrated to dry. The residual material was triturated with water, filtered, washed  
with water, acetonitrile and ethyl acetate, and dried to give example 363 (92 mg,  
80%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.44 (m, 1H), 1.72 (m, 1H), 2.41 (m, 1H),

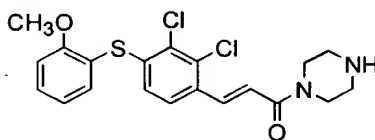
2.70 (t, 1H), 3.00 (m, 2H), 3.20 (m, 2H), 3.27 (m, 2H), 3.50 (m, 2H), 3.90 (s, 3H),  
 4.18 (br d, 1H), 4.40 (br d, 1H), 4.50 (t, 1H), 4.77 (d, 1H), 6.40 (d, 1H), 6.58 (d, 1H),  
 7.19 (d, 1H), 7.35 (d, 1H), 7.50 (d, 1H), 7.66 (d, 1H), 7.70 (m, 2H), 7.80 (t, 1H), 7.88  
 (s, 1H). MS (ESI<sup>+</sup>)  $m/z$  562 (M+H)<sup>+</sup>. Anal. calcd for C<sub>27</sub>H<sub>29</sub>Cl<sub>2</sub>N<sub>3</sub>SO<sub>4</sub>·0.25H<sub>2</sub>O:

5 C, 57.19; H, 5.24; N, 7.41. Found: C, 57.07; H, 5.22; N, 7.13.



Example 364

10 (2-Methoxyphenyl) [2,3-dichloro-4-(E-(4-(2,3-dihydroxypropionyl)piperazin-1-yl)carbonyl)ethenyl]phenyl sulfide

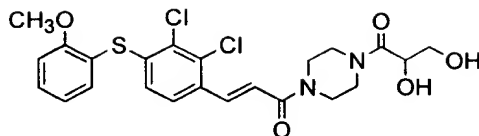


Example 364A

15 (2-Methoxyphenyl) [2,3-dichloro-4-(E-((piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 340G substituting methyl isonipecotate with piperazine. MS (DCI/NH<sub>3</sub>)  $m/e$  423 (M+H)<sup>+</sup>.

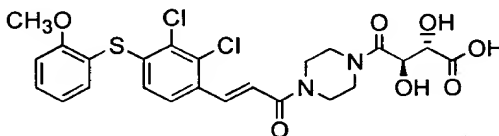
311

Example 364B

(2-Methoxyphenyl) [2,3-dichloro-4-( E-(4-(2,3-dihydroxypropionyl)piperazin-1-yl)carbonyl)ethenyl]phenyl sulfide

5 The title compound was prepared by the procedures described in Example 340, substituting methyl isonipecotate with Example 364A and substituting Example 340G with DL-glyceric acid Ca salt.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  3.2-3.8 (m, 12H), 4.38 (t, 1H), 6.58 (d, 1H), 7.10 (t, 1H), 7.27 (d, 1H), 7.28 (d, 1H), 7.50 (d, 1H), 7.60 (t, 1H), 7.79 (d, 1H), 7.83 (d, 1H). MS (ESI $^+$ )  $m/z$  511 (M+H) $^+$ .

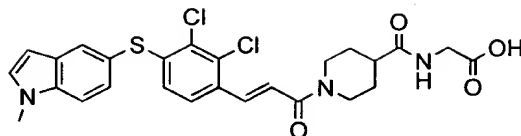
10

Example 365

(2-Methoxyphenyl) [2,3-dichloro-4-( E-(4-(2,3-dihydroxy-3-carboxypropionyl)piperazin-1-yl)carbonyl)ethenyl]phenyl sulfide

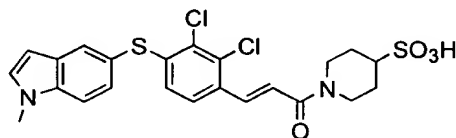
15 The title compound was prepared by the procedures described in Example 340 substituting methyl isonipecotate with Example 364A and substituting Example 340G with meso-tartaric acid.  $^1\text{H}$  NMR (300 MHz, CDCl $_3$ )  $\delta$  3.70 (m, 8H), 4.33 (br s, 1H), 4.72 (br s, 1H), 6.58 (d, 1H), 6.77 (d, 1H), 7.03 (m, 2H), 7.25(d, 1H), 7.50 (d, 1H), 7.52 (d, 1H), 8.00 (d, 1H). MS (ESI $^+$ )  $m/z$  555 (M+H) $^+$ .

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Example 366

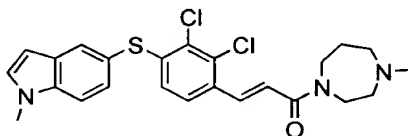
(1-Methylindol-5-yl) [2,3-dichloro-4-(E-((4-(carboxymethylamino)carbonyl)-  
piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 363 substituting 3-amino-1,2-propanediol with glycine methyl ester hydrochloride followed by hydrolysis. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.42 (m, 2H), 1.75 (m, 2H), 2.45 (m, 1H), 2.78 (m, 1H), 3.10 (m, 1H), 3.72 (d, 2H), 3.90 (s, 3H), 4.18 (br d, 1H), 4.40 (br d, 1H), 6.42 (d, 1H), 6.57 (d, 1H), 7.18 (d, 1H), 7.32 (d, 1H), 7.50 (d, 1H), 7.65 (d, 1H), 7.67 (d, 1H), 7.70 (m, 1H), 7.88 (s, 1H), 8.18 (t, 1H). MS (ESI<sup>+</sup>) *m/z* 546 (M+H)<sup>+</sup>. Anal. calcd for C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>Cl<sub>2</sub>SO<sub>4</sub>: C, 57.15; H, 4.61; N, 7.69. Found: C, 57.17; H, 4.64; N, 7.39.

Example 367

(1-Methylindol-5-yl) [2,3-dichloro-4-(E-((4-sulfopiperidin-1-  
yl)carbonyl)ethenyl)phenyl] sulfide

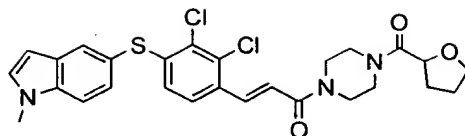
The title compound was prepared from Example 340F, by the procedures described in Example 340G, substituting methyl isonipecotate with piperidine-4-sulfonic acid.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.40 (m, 2H), 1.90 (m, 2H), 3.03 (m, 1H), 4.10 (m, 3H), 4.42 (br d, 1H), 6.40 (d,  $J=8.8\text{Hz}$ , 1H), 6.53 (d,  $J=3.1\text{Hz}$ , 1H), 7.15 (d,  $J=15.3\text{Hz}$ , 1H), 7.33 (dd,  $J=8.5$ ,  $1.7\text{Hz}$ , 1H), 7.48 (d,  $J=3.1\text{Hz}$ , 1H), 7.65 (d,  $J=8.5\text{Hz}$ , 1H), 7.67 (d,  $J=15.2\text{Hz}$ , 1H), 7.74 (d,  $J=8.8\text{Hz}$ , 1H), 7.87 (d,  $J=1.5\text{Hz}$ ). MS (ESI $^+$ )  $m/z$  525 (M+H) $^+$ . Anal. calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{Cl}_2\text{S}_2\text{O}_4 \cdot 0.8 \text{ TFA}$ : C, 47.91; H, 3.73; N, 4.54. Found: C, 47.71; H, 3.84; N, 4.73.



Example 368

(1-Methylindol-5-yl) [2,3-dichloro-4-(E-(4-methylhomopiperazin-1-ylcarbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 340G substituting methyl isonipecotate with N-methyl homopiperazine.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  2.06 (m, 2H), 2.81 (m, 2H), 3.17 (m, 2H), 3.55 (m 3H), 3.70 (s, 3H), 3.86 (s, 3H), 4.05 (m, 1H), 6.42 (dd,  $J=8.4, 3.3\text{Hz}$ , 1H), 6.54 (d,  $J=3.0\text{Hz}$ , 1H), 7.08 (dd,  $J=15.4, 7.5\text{Hz}$ , 1H), 7.35 (dd,  $J=8.8, 2.0\text{Hz}$ , 1H), 7.49 (d,  $J=3.0\text{Hz}$ , 1H), 7.65 (d,  $J=8.5\text{Hz}$ , 1H), 7.73 (d,  $J=8.8\text{Hz}$ , 1H), 7.80 (d,  $J=15.2\text{Hz}$ , 1H), 7.88 (d,  $J=2.0\text{Hz}$ , 1H). MS (ESI $^+$ )  $m/z$  474 (M+H) $^+$ . Anal. calcd for  $\text{C}_{26}\text{H}_{26}\text{N}_3\text{Cl}_2\text{SF}_3\text{O}_3 \cdot 0.75 \text{ TFA}$ : C, 49.01; H, 4.00; N, 6.23. Found: C, 48.71; H, 4.09; N, 6.13.

Example 369

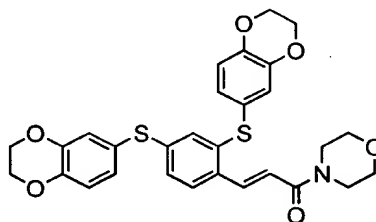
(1-Methylindol-5-yl) [2,3-dichloro-4-(E-(4-tetrahydrofuroyl)piperazin-1-yl)carbonyl]ethenyl]phenyl] sulfide

5

The title compound was prepared by the procedures described in Example

340G substituting methyl isonipecotate with 1-tetrahydrofuroylpiperazine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.80 (m, 2H), 2.00 (m, 2H), 3.50 (m, 8H), 3.75 (m, 2H), 3.88 (s, 3H), 4.68 (t, 1H), 6.42 (d, 1H), 6.57 (d, 1H), 7.19 (d, 1H), 7.32 (d, 1H), 7.48 (d, 1H), 7.65 (d, 1H), 7.70 (d, 1H), 7.75 (d, 1H), 7.87 (s, 1H). MS (ESI<sup>+</sup>) *m/z* 544 (M+H)<sup>+</sup>. Anal calcd for C<sub>27</sub>H<sub>27</sub>N<sub>3</sub>Cl<sub>2</sub>SO<sub>3</sub>: C, 59.56; H, 4.99; N, 7.71. Found: C, 59.40; H, 4.94; N, 7.61.

10

Example 370

(Benzodioxan-6-yl) [2-(benzodioxan-6-thioxy)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl] sulfide

15

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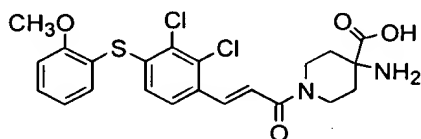
Sub  
A 104

Example 370A(E)-Morpholino 2,4-difluorocinnamide

The title compound was processed as reported in Example 1C substituting morpholine (1.04 mL, 11.9 mmol) for the amine and *trans*-2,4-difluorocinnamic acid (1.00 g, 5.4 mmol) for the carboxylic acid. The title compound was obtained as an off-white foam (1.4 g, 100%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 8.04 (dd, J=15.26, 8.82 Hz, 1H), 7.53 (d, J=14.91 Hz, 1H), 7.38-7.30 (m, 1H), 3.61-3.48 (m, 8H). MS (APCI) *m/z* 254 (M+H)<sup>+</sup>.

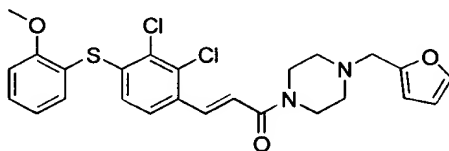
Example 370BMorpholinyl-(E)-2,4-bis(1,4-benzodioxane-6-mercaptan)cinnamic amide

Example 370A (233 mg, 1.00 mmol) was combined with cesium carbonate (652 mg, 2.00 mmol), 1,4-benzodioxane-6-thiol (370 mg, 2.20 mmol), and DMF (5 mL). The mixture was processed as reported in Example 1A to provide the title compound (220 mg, 40%) as a white foam. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.83 (d, J=15.20 Hz, 1H), 7.80 (d, J=8.20 Hz, 1H), 7.17 (d, J=15.3 Hz, 1H), 7.02 (dd, J=8.5, 2.0 Hz, 1H), 6.87-6.75 (m, 6H), 6.48 (s, 1H), 4.33-4.25 (m, 8H), 3.61-3.48 (m, 8H). MS (APCI) *m/z* 550 (M+H)<sup>+</sup>.

Example 371

(2-Methoxyphenyl) [2,3-dichloro-4-(*E*-((4-amino-4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

To a suspension of Example 355 (700 mg, 1.4 mmol) in DME (10 mL) was added a solution of (BOC)<sub>2</sub>O (1.51 g, 6.9 mmol) in DME (5 mL), triethylamine (0.23 mL, 1.7 mmol) and DMAP (9 mg, 0.07 mmol). The reaction mixture was stirred at room temperature overnight. Additional triethylamine (0.23 mL) and DMAP (30 mg) were added, and the mixture was heated at 60 °C for 6 hours. After aqueous work up, the crude product was suspended in DME (5 mL) and water (5 mL) containing 200 mg of NaOH. The suspension was stirred for 5 hours at room temperature, and separated by HPLC to give the title compound (300 mg, 45%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.78 (m, 2H), 2.10 (m, 2H), 3.60 (m, 2H), 3.80 (s, 3H), 3.86 (m, 2H), 6.58 (d, 1H), 7.10 (d, 1H), 7.25 (d, 1H), 7.28 (d, 1H), 7.50 (d, 1H), 7.58 (t, 1H), 7.77 (d, 1H), 7.80 (d, 1H), 8.50 (br s, 2H). MS (ESI<sup>+</sup>) *m/z* 481 (M+H)<sup>+</sup>. Anal calcd for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>Cl<sub>2</sub>SO<sub>4</sub>·0.75 H<sub>2</sub>O: C, 47.34; H, 4.06; N, 4.60. Found: C, 47.31; H, 4.05; N, 4.43.

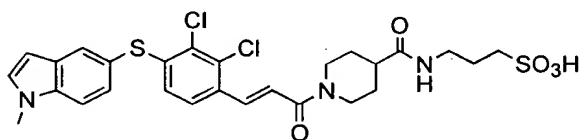


Example 372

(2-Methoxyphenyl)[2,3-dichloro-4-((4-furoylpiperazin-1-yl)carbonyl)ethenyl]phenyl] sulfide

506  
105

To a solution of Example 364A (100mg, 0.24 mmol) and 2-furfural (30mg, 0.24 mmol) in dichloroethane (2 mL) was added NaBH(OAc)<sub>3</sub> (142 mg, 0.67 mmol) under nitrogen atmosphere. The mixture was stirred for 16 hours at room temperature. Dichloromethane (20 mL) was added and the mixture was washed with 5% NaHCO<sub>3</sub>, then with brine, and the organic phase was separated and concentrated. The residual solid was chromatographed by flash chromatography (5% MeOH/CH<sub>2</sub>CL<sub>2</sub>) and desired fractions were combined, concentrated and dried to afford the title compound as an off-white solid (84 mg, 69%). HPLC (Supelco C-18 column, water:acetonitrile 100:0- 0:100, 15 minute elution, flow rate 1.5 mL/min) rt 11.90 min. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.39 (m, 4H), 3.52 (s, 2H), 3.55 (m, 2H), 3.63 (m, 2H), 3.79 (s, 3H), 6.29 (d, 1H), 6.40 (m, 1H), 6.57 (d, 1H), 7.08 (dt, 1H), 7.21 (d, 1H), 7.23 (dd, 1H), 7.48 (dd, 1H), 7.57 (m, 2H), 7.72 (d, 1H), 7.80 (d, 1H). MS (ESI) *m/e* 503 (M+H)<sup>+</sup>.



### Example 373

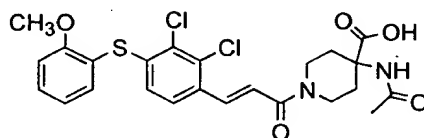
(1-Methylindol-5-yl) [2,3-dichloro-4-( E-(4-(carbo-3-sulfopropylamino)piperidin-1-yl)carbonyl)ethenyl]phenyl] sulfide

The title compound was prepared from Example 340H by the procedures described in Example 363 substituting 3-amino-1,2-propanediol with 3-amino-1-propanesulfonic acid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.40 (m, 2H), 1.70 (m, 4H),

2.38 (m, 1H), 2.42 (m, 2H), 2.70 (m, 1H), 3.05 (m, 3H), 3.86 (s, 3H), 4.18 (br d, 1H), 4.40 (br d, 1H), 6.40 (d, 1H), 6.55 (d, 1H), 7.20 (d, 1H), 7.35 (d, 1H), 7.50 (d, 1H), 7.65 (d, 1H), 7.70 (d, 1H), 7.77 (d, 1H), 7.87 (d, 1H). MS (ESI<sup>+</sup>) *m/z* 610 (M+H)<sup>+</sup>.

Anal calcd for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>Cl<sub>2</sub>S<sub>2</sub>O<sub>5</sub>·1.5 TFA: C, 46.10; H, 3.93; N, 5.38. Found: C,

5 46.52; H, 4.03; N, 5.66.



Example 374

(2-Methoxyphenyl)[2,3-dichloro-4-(E-(4-acetylaminopiperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide

10

To a suspension of Example 371 (90 mg, 0.187 mmol) and triethylamine (0.08 mL, 0.57 mmol) in DMF (3 mL) was added acetyl chloride (0.1 mL) at room temperature. The mixture was stirred for 3 hours. Ethyl acetate (60 mL) was added, and the mixture was washed with brine. The organic phase was dried, filtered and concentrated. The residue was separated by HPLC (C-18, CH<sub>3</sub>CN/H<sub>2</sub>O) to give example 374 (56 mg, 57%).

15

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.78 (m, 2H), 1.82 (s, 3H), 1.98 (m, 2H), 3.05 (t, 1H), 3.38 (t, 1H), 3.80 (s, 3H), 4.00 (br d, 1H), 4.12 (br d, 1H), 6.58 (d, 1H), 7.08 (t, 1H), 7.23 (d, 1H), 7.25 (d, 1H), 7.50 (d, 1H), 7.58 (t, 1H), 7.78 (d, 1H), 7.80 (d, 1H),

20

8.18 (s, 1H). MS (ESI<sup>+</sup>) *m/z* 523 (M+H)<sup>+</sup>. Anal calcd for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>Cl<sub>2</sub>SO<sub>5</sub>·0.35TFA: C, 52.80; H, 4.40; N, 5.05. Found: C, 52.74; H, 4.42; N, 5.11.

Example 375

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

5        The title compound was prepared by the procedures described in Example 352, employing the compound of Example 359D to give a white solid. <sup>1</sup>H NMR(CD<sub>3</sub>OD, 300 MHz) δ 1.65 (br s, 2H), 1.94-2.03 (m, 2H), 2.57-2.67 (m, 1H), 2.95-3.05 (m, 1H), 3.23-3.32 (m, 1H), 3.75 (s, 3H), 4.12 (br s, 1H), 4.40 (br s, 1H), 7.00 (d, J=15Hz, 1H), 7.03-7.20 (m, 3H), 7.47-7.53 (m, 2H), 7.68 (d, J=9Hz, 1H), 7.77 (qq, J=15Hz, 10    1H). MS (ESI) *m/z* 534 (M+H)<sup>+</sup>. Anal calcd for C<sub>24</sub>H<sub>21</sub>NF<sub>6</sub>O<sub>4</sub>S: C, 54.03; H, 3.97; N, 2.63. Found: C, 54.11; H, 4.04; N, 1.76.

Example 376

(2-Methoxyphenyl) 5-[8-(E-((4-(aminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)quinolinyl]sulfide

15

Example 376A

5-Chloro-8-(trifluoromethanesulfonyloxy)quinoline

5-Chloro-8-hydroxyquinoline was treated as described in Example 340E to provide 20    the title compound. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.59 (7.5Hz, 1H), 7.65-7.69 (m, 2H), 8.63 (dd, J<sub>1</sub>=9Hz, J<sub>2</sub>=1.5Hz, 1H), 9.21 (dd, J<sub>1</sub>=6Hz, J<sub>2</sub>=1.5Hz, 1H). MS (APCI-NH<sub>3</sub>) *m/e* 312, 314 (M+H)<sup>+</sup>.

Example 376B5-Chloro-8-[E-(methoxycarbony)ethenyl]quinoline

The method of Example 340D was used, substituting the product from Example 376A for Example 340C. Thus, Example 376A (6.23 g, 20.0 mmol) was converted to the title compound (2.22 g, 45%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 3.78 (s, 3H), 6.98 (d, J=16.5Hz, 1H), 7.78-7.83 (m, 1H), 7.88 (d, J=9Hz, 1H), 8.32 (d, J=9Hz, 1H), 8.65 (dd, J<sub>1</sub>=9Hz, J<sub>2</sub>=1.5Hz, 1H), 8.85 (d, J=16.5 Hz, 1H), 9.12 (dd, J<sub>1</sub>=4.5Hz, J<sub>2</sub>=1.5Hz, 1H). MS (APCI-NH<sub>3</sub>) *m/e* 248, 250 (M+H)<sup>+</sup>.

Example 376C(2-Methoxyphenyl) 5-[8-(E-(methoxycarbonyl)ethenyl)quinolinyl]sulfide

The method of Example 340F was used, substituting the product from Example 376B for Example 340E. Thus, Example 376B (2.19 g, 8.84 mmol) was converted to the title compound (1.07 g, 36%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 3.83 (s, 3H), 6.80 (d, J=16.5Hz, 1H), 6.86-6.99 (m, 2H), 7.16 (d, J=6Hz, 1H), 7.33-7.38 (m, 1H), 7.44 (d, J=7.5Hz, 1H), 7.67-7.72 (m, 1H), 8.22 (d, J=7.5Hz, 1H), 8.63 (dd, J<sub>1</sub>=9Hz, J<sub>2</sub>=1.5Hz, 1H), 8.82 (d, J=16.5Hz, 1H), 9.07 (dd, J<sub>1</sub>=6Hz, J<sub>2</sub>=1.5Hz), 12.48 (s, 1H). MS (APCI-NH<sub>3</sub>) *m/e* 338 (M+H)<sup>+</sup>.

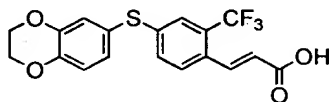
Example 376C(2-Methoxyphenyl) 5-[8-(E-((4-(aminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)quinolinyl]sulfide

The method of Example 340G was used, substituting the product from Example 376B for Example 340F, and substituting 4-piperidinecarboxamide for methyl

isonipecotate.  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  1.71-2.82 (m, 2H), 2.96-2.03 (m, 2H), 2.44-2.52 (m, 1H), 2.81-2.94 and 3.16-3.30 (m, 1H), 3.37-3.54 (m, 2H), 3.88 (s, 3H), 4.17-4.34 and 4.60-4.80 (m, 1H), 5.72 (s, 2H), 6.82 (t, 4.5Hz, 1H), 6.90 (dd,  $J_1=4.5\text{Hz}$ ,  $J_2=0.75\text{Hz}$ , 1H), 6.93 (d, 6Hz, 1H), 7.23-7.28 (m, 1H), 7.40 (d,  $J=9\text{Hz}$ , 1H), 7.47-7.50 (m, 1H), 7.51 (d,  $J=6\text{Hz}$ , 1H), 7.82 (d,  $J=4.5\text{ Hz}$ , 1H), 8.57 (d,  $J=9\text{Hz}$ , 1H), 8.74 (dd,  $J_1=4.5\text{Hz}$ ,  $J_2=0.75\text{Hz}$ , 1H), 9.00 (m, 1H).

#### Example 377

(2-Methoxyphenyl) [2-trifluoromethyl-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

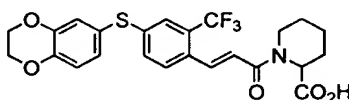


#### Example 377A

2-Trifluoromethyl-4-(thiobenzodioxan-6-yl)cinnamic acid

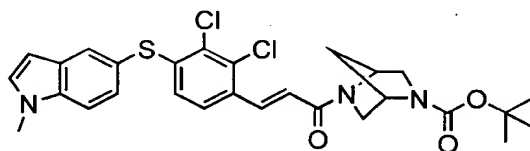
A solution of commercially available 4-fluoro-2-(trifluoromethyl)cinnamic acid (5 g, 21.4 mmol) in ethyl acetate (200 mL) under nitrogen at ambient temperature was treated with a solution of diazomethane in diethyl ether to a persistent yellow color, stirred an additional ten minutes, then quenched by dropwise addition of glacial acetic acid. The resultant clear solution was washed with saturated  $\text{NaHCO}_3$ ,

brine, dried ( $\text{MgSO}_4$ ), filtered through a plug of silica, rinsed with ethyl acetate and concentrated to give 5.4 grams of a yellow oil. A solution of this methyl ester (2.5 g, 10 mmol) and 6-mercaptobenzodioxane (1.9 g, 11 mmol) in 40 mL of dimethylformamide was treated with cesium carbonate (3.9 g, 12 mmol), and stirred  
5 at room temperature for 20 hours. The resultant orange heterogeneous solution was diluted with diethyl ether and water, washed with 1 M NaOH, distilled water, brine, dried ( $\text{MgSO}_4$ ), filtered through a plug of silica, concentrated and then flash chromatographed with 20% ethyl acetate/hexane followed by 33% ethyl acetate/hexane to give 2.8 g of a light yellow syrup. A solution of this diaryl sulfide  
10 ester (2.8 g, 7.1 mmol) in THF (21 mL) and distilled water (7 mL) was treated with lithium hydroxide hydrate (450 mg, 10.7 mmol) and stirred 67 hours at ambient temperature. The resultant solution was diluted with distilled water, washed with diethyl ether, acidified to pH 1-2 with 3 M  $\text{H}_2\text{SO}_4$ , extracted with diethyl ether, washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated to give 2.7 g (7.1 mmol) of the  
15 title compound as an off-white powder (71%).  $^1\text{H}$  NMR (300 MHz,  $\text{d}_6\text{-DMSO}$ )  $\delta$  7.97 (d, 1H), 7.72 (dq, 1H), 7.47 (d, 1H), 7.31 (dd, 1H), 7.05 (m, 3H), 6.58 (d, 1H), 4.3 (m, 4H). MS (APCI- $\text{NH}_3$ )  $m/e$  383 ( $\text{M}+\text{H}$ ) $^+$ , 400 ( $\text{M}+\text{NH}_4$ ) $^+$ .

Example 377B

(Benzodioxan-6-yl)[3-trifluoromethyl-4-(E-((2-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

Example 377A (382 mg, 1 mmol) was coupled with (d,l)-ethyl picipolate according to the procedure of Example 340G. The derived ethyl ester was hydrolyzed using the method of Example 340H to give 280 mg of the title compound as a light yellow foam (84%). Analytical HPLC: 4.6X250 mm C18 column, 0.8 mL/min, 254 nm, CH<sub>3</sub>CN:H<sub>2</sub>O with 0.1% TFA, 0:100 (0 min), ramp to 90:10 (0-10 min), 90:10 (10-18 min), ramp to 0:100 (18-20 min), rt 11.29 min (98.2 area%). <sup>1</sup>H NMR (300 MHz, d<sub>6</sub>-DMSO) δ 8.07 (t, 1H), 7.65 (dq, 1H), 7.38 (m, 3H), 7.03 (m, 3H), 5.15 (m, 1H), 4.4 (m, 1H), 4.29 (m, 4H), 4.1 (m, 1H), 3.2 (m, 1H), 2.2 (m, 1H), 1.68 (m, 2H), 1.3 (m, 2H). MS (APCI-NH<sub>3</sub>) *m/e* 494 (M+H)<sup>+</sup>, 511 (M+NH<sub>4</sub>)<sup>+</sup>.



Example 378

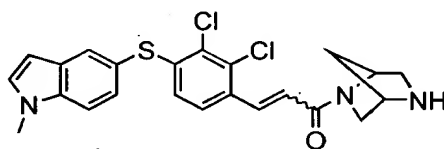
(1-Methylindol-5-yl)[2,3-dichloro-4-(E-(((1S,4S)-5-tert-butyloxycarbonyl-2,5-diazabicyclo(2,2,1)heptan-2-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 340 substituting methyl isonipecotate with t-butyl (1S,4S)-(-)-2,5-diazabicyclo(2,2,1)heptane-2-carboxylate. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.40 (s, 9H), 1.82 (m, 2H), 3.17 (m, 1H), 3.30 (m, 2H), 3.58 (m, 1H), 3.82 (s, 3H), 4.05 (m,

324

Sub A107  
 1H), 4.40 (m, 1H), 4.75 (br s, 1H), 4.92 (br s, 1H), 6.42 (dd, 1H), 6.58 (d, 1H), 6.75 (d, 1H), 7.05 (d, 1H), 7.35 (d, 1H), 7.50 (d, 1H), 7.65 (d, 1H), 7.68 (d, 1H), 7.78 (t, 1H), 7.77 (s, 1H). MS (ESI<sup>+</sup>)  $m/z$  558 (M+H)<sup>+</sup>. Anal calcd for C<sub>28</sub>H<sub>29</sub>N<sub>3</sub>Cl<sub>2</sub>SO<sub>3</sub>: C, 60.21; H, 5.23; N, 7.52. Found: C, 60.23; H, 5.36; N, 7.41.

5

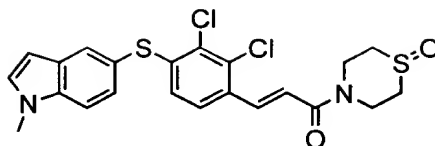
Example 379

Sub A108  
(1-Methylindol-5-yl) [2,3-dichloro-4-(E/Z-((1S,4S)-2,5-diazabicyclo(2.2.1)heptan-2-ylcarbonyl)ethenyl)-2,3-dichlorophenyl] sulfide

- 10 To a solution of Example 378 (820 mg, 1.47 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added trifluoroacetic acid (2mL) at 0°C. The yellow solution was stirred at the same temperature for 2 hours. More CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added and the solution was poured into water (100 mL) containing NaHCO<sub>3</sub> (4.5 g). The insoluble material was collected by filtration, washed with water and methanol. The CH<sub>2</sub>Cl<sub>2</sub> solution was
- 15 concentrated, and the residual solid was filtered, washed with water, methanol and CH<sub>2</sub>Cl<sub>2</sub>. The combined solid was dried to give the title compound (650 mg, 95%).
- <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.70 (m, 2H), 2.90 (m, 1H), 3.50 (m, 4H), 3.88 (s, 3H), 4.85 (m, 1H), 6.45 (d, 1H), 6.60 (dd, 1H), 6.77 (d, 1H), 7.05 (dd, 1H), 7.25 (s, 1H), 7.35 (dd, 1H), 7.65 (d, 1H), 7.70 (d, 1H), 7.80 (d, 1H). MS (ESI<sup>+</sup>)  $m/z$
- 20 458(M+H)<sup>+</sup>.

(1-Methylindol-5-yl) [2,3-dichloro-4-(*E*-(4-hydroxy-3-carboxypiperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide

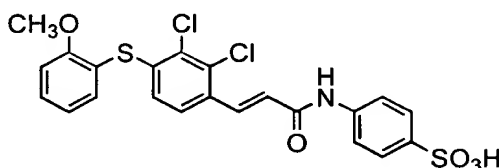
180 mg of this solid was dissolved in THF (10 mL). A solution of lithium hydroxide monohydrate (29 mg, 0.68 mmol) in water (10 mL) was added. The mixture was stirred at room temperature 2 hours, NaBH<sub>4</sub> (50 mg) was then added. After 4 hours stirring, the solution was acidified and concentrated to 5 mL. The formed white solid was collected by filtration, washed with water, acetonitrile, and dried to give the title compound (92 mg). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.60 (m, 2H), 3.00 (m, 1H), 3.40 (m, 1H), 3.85(1H, 4.05 (m, 1H), 4.20 (m, 1H), 4.35 (m, 1H), 5.00 (m, 1H), 6.42 (d, 1H), 6.58 (d, 1H), 7.20 (dd, 1H), 7.35 (d, 1H), 7.50 (d, 1H), 7.6-7.8 (m, 3H), 7.90 (s, 1H). MS (ESI<sup>+</sup>) *m/z* 505 (M+H)<sup>+</sup>. Anal calcd for C<sub>24</sub>H<sub>27</sub>N<sub>2</sub>Cl<sub>2</sub>SO<sub>4</sub>: C, 57.03; H, 4.38; N, 5.54. Found: C, 56.77; H, 4.17; N, 5.34.

Example 381

(1-Methylindol-5-yl) [2,3-dichloro-4-( E-(S-oxothiomorpholin-1-

5 ylcarbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 340 substituting methyl isonipecotate with thiomorpholine S-oxide. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.70 (m, 2H), 2.85 (m, 2H), 3.85 (s, 3H), 3.90 (m, 2H), 4.20 (m, 1H), 4.60 (m, 1H), 6.45 (d, 1H), 6.55 (d, 1H), 6.70 (d, 1H), 7.18 (d, 1H), 7.20 (d, 1H), 7.38 (d, 10 1H), 7.41 (d, 1H), 7.77 (s, 1H), 7.98 (d, 1H). MS (ESI<sup>+</sup>) *m/z* 479 (M+H)<sup>+</sup>.

Example 382

(2-Methoxyphenyl) [2,3-dichloro-4-( E-((4-

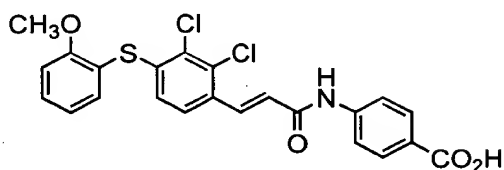
15 sulfophenylamino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-( E-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with sulfanilic acid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 3.82 (s, 3H), 6.65 (d, 1H), 6.82 (d, 1H), 7.12

(t, 1H), 7.25 (d, 1H), 7.5-7.7 (m, 7H), 7.85 (d, 1H), 10.40 (s, 1H). MS (ESI<sup>+</sup>) *m/z* 510

(M+H)<sup>+</sup>. Anal calcd for C<sub>22</sub>H<sub>17</sub>Cl<sub>2</sub>NS<sub>2</sub>O<sub>5</sub>·0.65TFA: C, 50.80; H, 3.25; N, 2.55.

Found: C, 50.75; H, 3.43; N, 2.65.

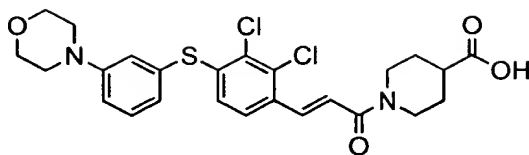


Example 383

(2-Methoxyphenyl) [2,3-dichloro-4-( E-((4-carboxyphenylamino)carbonyl)ethenyl)phenyl] sulfide

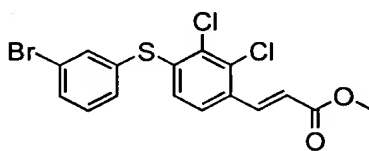
The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-( E-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with 4-aminobenzoic acid. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 3.82 (s, 3H), 6.65 (d, 1H), 6.82 (d, 1H), 7.10 (t, 1H), 7.30 (d, 1H), 7.60 (m, 3H), 7.82 (t, 3H), 7.90 (d, 1H), 7.92 (d, 1H), 10.65 (s, 1H), 12.75 (s, 1H). MS (ESI<sup>+</sup>) *m/z* 474 (M+H)<sup>+</sup>.

328

Example 384

[3-(4-Morpholino)phenyl] [2,3-dichloro-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

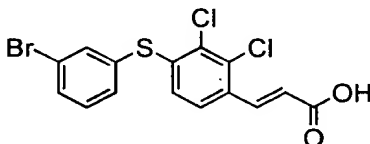
5

Example 384A

10 (3-Bromophenyl) [2,3-dichloro-4-(E-[methoxycarbonyl]ethenyl)phenyl] sulfide

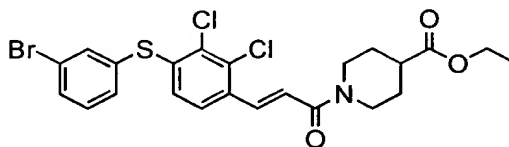
Sub  
Allo

To a solution of the resultant compound from Example 340E (12.0 g, 31.7 mmol) in N-methylpyrrolidinone (63 mL) at 0 °C (under dry N<sub>2</sub>) was added 3-bromothiophenol (4.0 mL, 7.3 g, 38.8 mmol) and a solution of lithium *tert*-butoxide (3.1 g, 38.8 mmol), and the resulting solution was stirred for 3 h at 0 °C. The reaction was diluted with 500 mL EtOAc and extracted sequentially with 100 mL water, 3 x 60 mL of 1 N aq. NaOH, then 2 x 100 mL brine. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to produce the crude title compound (9.2 g). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 3.75 (s, 3H), 6.67 (d, J=15 Hz, 1H), 6.83 (d, J=9 Hz, 1H), 7.46-7.59 (m, 2H), 7.72-7.76 (m, 2H), 7.80 (t, J=2.5 Hz, 1H), 7.85 (d, J=9 Hz, 1H), 7.88 (d, J=15 Hz, 1H); MS (APCI) *m/e* 419 (M+H)<sup>+</sup>.



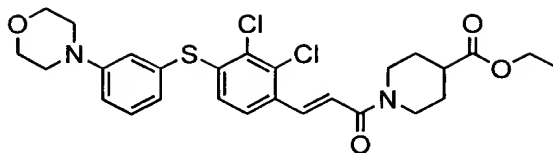
Example 384B(3-Bromophenyl) [2,3-dichloro-4-(*E*-carboxyethenyl)phenyl] sulfide

Using the procedure for Example 340H, Example 348A was hydrolyzed to the title compound. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 6.56 (d, J=16.5 Hz, 1H), 6.84 (d, J=9 Hz, 1H), 7.45-7.58 (m, 2H), 7.72 (m, 1H), 7.77-7.86 (m, 4H), 12.75 (br s, 1H); (ESI) *m/e* 401, 403 (M-H)<sup>+</sup>.

Example 384C(3-bromophenyl) [2,3-dichloro-4-(*E*-[(4-ethoxycarbonylpiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

The title compound (750 mg, 58%) was prepared from Example 384B (1.0 g, 2.48 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with ethyl isonipecotate. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.18 (t, J=7.5 Hz, 3H), 1.38-1.56 (m, 2H), 1.82-1.92 (m, 2H), 2.50-2.69 (m, 1H), 2.80-2.93 (m, 1H), 3.14-3.27 (m, 1H), 4.07 (t, J=7.5 Hz, 2H), 4.10-4.35 (m, 2H), 6.92 (d, J=9 Hz, 1H), 7.30 (d, J=15 Hz, 1H), 7.43-7.52 (m, 2H), 7.67-7.77 (m, 3H), 7.92 (d, J=9 Hz, 1H).

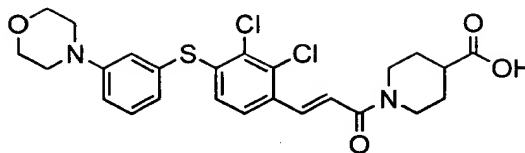
330

Example 384D

[3-(4-Morpholino)phenyl] [2,3-dichloro-4-(E-[(4-ethoxycarbonyl)piperidin-1-yl]carbonyl]ethenyl)phenyl] sulfide

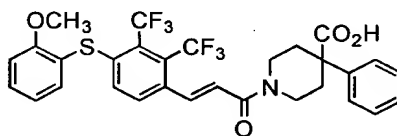
5 The procedure of D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* 1998, 120, 9722-9723, was adapted. To a stirred solution of Example 384D (180 mg, 0.331 mmol) in ethylene glycol dimethyl ether (1 mL) containing 1-(N,N-dimethylamino)-1'-(dicyclohexylphosphino)biphenyl (7 mg, 5 mol%), Pd<sub>2</sub>(dba)<sub>3</sub> (8 mg, 2.5 mol%), and morpholine (0.058 ml, 0.663 mmol) was added powdered K<sub>3</sub>PO<sub>4</sub> 10 (141 mg, 0.663 mmol). The reaction mixture was bubbled with N<sub>2</sub> for 5 min and heated at 90 °C in sealed tube for 18 h. Then the solvent was removed under reduced pressure and residue was diluted with methylene chloride (1 mL). The title compound (90 mg, 50%) was isolated by flash chromatography on silica gel eluting with 20% acetone-hexane. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 1.18 (t, J=7.5 Hz, 3H), 1.35-1.55 (m, 2H), 1.79-1.91 (m, 2H), 2.58-2.69 (m, 1H), 2.70-2.94 (m, 2H), 3.16 (t, J=4.5 Hz, 2H), 3.15 (t, J=5 Hz, 4H), 3.73 (t, J=4.5 Hz, 4H), 3.78 (t, J=5 Hz, 2H), 4.08 (q, J=7.5 Hz, 2H), 4.11-4.36 (m, 2H), 6.70 (d, J=8.25 Hz, 1H), 6.97 (m, 1H), 7.10-7.27 (m, 2H), 7.24 (d, J=15 Hz, 1H), 7.39 (m, 1H), 7.73 (d, J=15 Hz, 1H), 7.86 (d, J=8.25 Hz, 1H); MS (ESI) *m/e* 549, 551 (M+H)<sup>+</sup>.

331

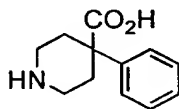
Example 384E

[3-(4-Morpholino)phenyl] [2,3-dichloro-4-(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

5 The title compound (38 mg, 67%) was prepared from Example 384D (60 mg, 0.11mmol) using the procedures described in Example 340H. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 1.37-1.55 (m, 2H), 1.81-1.90 (m, 2H), 2.52-2.58 (m, 1H), 2.80-2.94 (m, 1H), 3.10-3.15 (m, 3H), 3.67-3.75 (m, 3H), 3.76-3.99(m, 3H), 4.04-4.16 (M, 1H), 4.22-4.33 (m, 1H), 6.71 (d, J=8Hz, 1H), 6.96 (d, J=7Hz, 1H), 7.07 (m, 1H), 7.12 (s, 1H), 7.24 (d, J=15Hz, 1H), 7.38 (t, j=7Hz, 1H), 7.73 (d, J=15Hz, 1H), 7.85 (d, J=8Hz, 1H). MS (ESI) *m/e* 521, 523 (M+H)<sup>+</sup>, 519, 521 (M-H)<sup>-</sup>.

Example 385

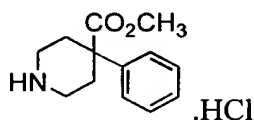
15 (2-Methoxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-phenylcarboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide



Example 385A4-Phenylpiperidine-4-carboxylic acid

Sub  
A112  
4-Cyano-4-phenylpiperidine hydrochloride (2.0g, 0.11 mol) was dissolved in 8 mL of conc.  $H_2SO_4$  and 4 mL of  $H_2O$ , then the solution was heated at reflux for 4 h.

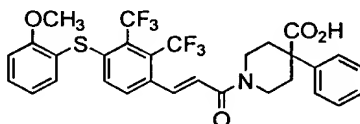
5 The solution was cooled and then NaOH was added to precipitate a white solid. The solid was collected, then dissolved in methanol, and the solution was filtered and concentrated to obtain a white solid. This dried solid was used for without purification for Example 385B.



10

Example 385BMethyl 4-phenylpiperidine-4-carboxylate hydrochloride

Dissolved the 4-phenylpiperidinecarboxylic acid in 10 mL of methanol and added 2 mL of thionyl chloride dropwise at room temperature. The resulting mixture  
15 was stirred overnight at room temperature. Evaporated solvent in vacuo, added toluene and evaporated excess thionyl chloride in vacuo. This white powder salt was used for next step without further purification.



20

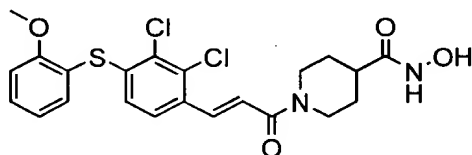
Example 385C

(2-Methoxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-phenylcarboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

Sub  
A113<sup>5</sup>

The methyl ester of the title compound was prepared by the procedures described in Example 356, employing the compound of Example 359D as starting material, to give an oil. The resultant methyl ester was hydrolyzed with aq. NaOH in methanol at 60 °C for 4 h to give a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz) δ 1.88 (br t, J=13.5 Hz, 2H), 2.59 (br d, J=13.5 Hz, 2H), 3.13 (br t, J=13.5 Hz, 1H), 3.75 (s, 3H), 3.44 (br t, J=13.5 Hz, 1H), 4.12 (br d, J=13.5 Hz, 1H), 4.42 (br d, J=13.5 Hz, 1H), 6.35 (d, J=15 Hz, 1H), 7.0-7.46 (m, 7H), 7.43-7.55 (m, 3H), 7.62-7.85 (m, 2H);

10 MS(ESI) *m/z* 610(M+H)<sup>+</sup>. Anal calcd for C<sub>30</sub>H<sub>25</sub>F<sub>6</sub>NO<sub>4</sub>S·H<sub>2</sub>O: C, 57.49; H, 4.13; N, 2.20. Found: C, 57.12; H, 3.93; N, 1.77.



Example 386

15 (2-Methoxyphenyl)[2,3-dichloro-4-(E-((4-hydroxylaminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

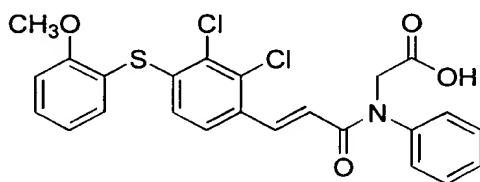
Sub  
A114

To a suspension of Example 319 (300 mg, 0.64 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added oxalyl chloride (67 μL) and 2 drops of DMF. The yellow suspension was stirred at room temperature for 2 h to give an orange solution which was then

20 concentrated under reduced pressure, and dried under vacuum. An aliquot of the resulting acid chloride solution (2 mL) was added to a solution containing o-

Sub  
All

trimethylsilyloxyamine (101 mg, 0.96 mmol), Hunig's base (122  $\mu$ L, 0.7 mmol) and DMAP (2 mg) in  $\text{CH}_2\text{Cl}_2$  (3 mL). After the solution was stirred at room temperature for 1 h, TBAF (1.0 M solution in THF, 1.5 mL) was then added. The brown solution was stirred at room temperature for another h, then it was purified by HPLC (Zorbax, C-18) to give the title compound as white solid (71 mg).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.50 (m, 2H), 1.70 (m, 2H), 2.28 (m, 1H), 2.70 (m, 1H), 3.09 (m, 1H), 3.79 (s, 3H), 4.23 (m, 1H), 4.45 (m, 1H), 6.55 (d,  $J = 8.8$  Hz, 1H), 7.08 (t,  $J = 7.4$  Hz, 1H), 7.25 (m, 2H), 7.48 (d,  $J = 7.2$  Hz, 1H), 7.54 (t,  $J = 8.2$  Hz, 1H), 7.73 (d,  $J = 15.3$  Hz, 1H), 7.82 (d,  $J = 8.8$  Hz, 1H), 8.55 (br s, 1H), 10.46 (s, 1H). MS (ESI $^+$ )  $m/z$  481 (M+H) $^+$ .



### Example 387

(2-Methoxyphenyl) [2,3-dichloro-4-(E-((N-carboxymethyl-N-phenylamino)carbonyl)ethenyl)phenyl] sulfide

Sub  
All

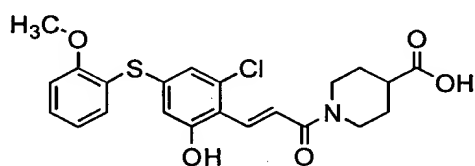
The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-(E-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with N-phenylglycine ethyl ester following by hydrolysis.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  3.76 (s, 3H), 4.40 (s, 2H), 6.35 (d,  $J = 15.5$  Hz, 1H), 6.46 (d,  $J = 8.4$  Hz, 1H), 7.05 (t,  $J$

335

Sub  
Alls

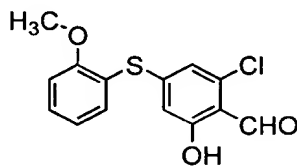
= 7.3 Hz, 1H), 7.22 (m, 2H), 7.35 (t,  $J = 7.5$  Hz, 3H), 7.44 (t,  $J = 7.2$  Hz, 3H), 7.55 (t,  $J = 7.4$  Hz, 1H), 7.76 (d,  $J = 15.4$  Hz, 1H); MS (ESI<sup>+</sup>)  $m/z$  488,490 (M+H)<sup>+</sup>. Anal. calcd for C<sub>24</sub>H<sub>19</sub>NCl<sub>2</sub>O<sub>4</sub>S: C, 59.02; H, 3.92; N, 2.87. Found: C, 58.71; H, 4.10; N, 2.58.

5

Example 388

(2-Methoxyphenyl) [3-chloro-6-hydroxy-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

10

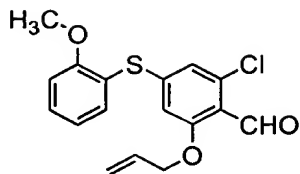
Example 388A

(2-Methoxyphenyl) ((3-chloro-6-hydroxy-4-formyl)phenyl)sulfide

2-Methoxythiophenol (3.5 mL, 28.9 mmol) and 2,4-dichoro-6-

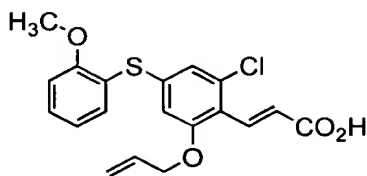
15 hydroxybenzaldehyde (5.00g, 26.3 mmol) were processed as described in Example 1 to provide the title disulfide (6.71 g, 87%) as a pale yellow solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  10.18 (s, 1H), 7.61 (dd,  $J=7.4$  Hz,  $J=1.7$  Hz, 1H), 7.56 (dd,  $J=7.7$  Hz,  $J=1.9$  Hz, 1H), 7.25 (d,  $J=7.3$  Hz, 1H), 7.11 (dt,  $J=7.7$  Hz,  $J=1.5$  Hz, 1H), 6.69 (d,  $J=1.8$  Hz, 1H), 6.38 (d,  $J=1.5$  Hz, 1H), 3.80 (s, 3H); MS (APCI)  $m/z$  294 (M+H)<sup>+</sup>.

00760" 56274560

Example 388B(2-Methoxyphenyl)(3-chloro-6-allyloxy-4-benzaldehyde)sulfide

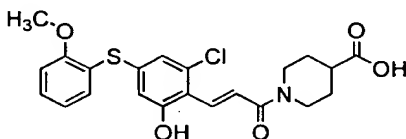
- 5 Allyl bromide (2.0 mL, 22.8 mmol) was added to a stirred solution of Example 388A (6.71 g, 22.8 mmol), cesium carbonate (14.86 g, 45.6 mmol), and DMF (45 mL). After 21 h, the pale yellow solution was diluted with 1 N aqueous HCl (100 mL) and extracted with Et<sub>2</sub>O (2x75 mL). The ether extracts were combined, dried (MgSO<sub>4</sub>), filtered, and concentrated to a yellow solid (7.20 g, 94%). <sup>1</sup>H NMR
- 10 (DMSO-d<sub>6</sub>, 300 MHz) δ 10.28 (s, 1H), 7.58 (dd, *J*=8.4 Hz, *J*=1.7 Hz, 1H), 7.52 (dd, *J*=7.8 Hz, *J*=1.7 Hz, 1H), 7.23 (d, *J*=8.1 Hz, *J*=1.0 Hz, 1H), 7.08 (dt, *J*=7.8 Hz, *J*=1.4 Hz, 1H), 6.82 (d, *J*=1.7 Hz, 1H), 6.52 (d, *J*=1.7 Hz, 1H), 5.97 (m, 1H), 5.33 (d, *J*=17.3 Hz, 1H), 5.28 (d, *J*=10.8 Hz, 1H), 4.61 (m, 2H), 3.80 (s, 3H); MS (APCI) *m/z* 335 (M+H)<sup>+</sup>.

337

Example 388C(2-Methoxyphenyl)[3-chloro-6-allyloxy-4-((carboxy)ethenyl)phenyl]sulfide

Example 388B was processed as detailed in Example 1B. <sup>1</sup>H NMR (DMSO-  
 5 d<sub>6</sub>, 300 MHz) δ 7.77 (d, *J*=16.3 Hz, 1H), 7.51 (dd, *J*=7.4 Hz, *J*=1.7 Hz, 1H), 7.43 (dd, *J*=7.4 Hz, *J*=1.7 Hz, 1H), 7.19 (dd, *J*=8.1 Hz, *J*=1.0 Hz, 1H), 7.05 (dt, *J*=7.4 Hz, *J*=1.4 Hz, 1H), 6.82 (d, *J*=1.3 Hz, 1H), 6.72 (d, *J*=15.9 Hz, 1H), 6.66 (d, *J*=1.7 Hz, 1H), 6.00 (m, 1H), 5.30 (d, *J*=9.8 Hz, 1H), 5.26 (d, *J*=3.1 Hz, 1H), 4.63 (m, 2H), 3.80 (s, 3H).  
 MS (APCI) *m/z* 377 (M+H<sup>+</sup>) 394 (M+NH<sub>4</sub><sup>+</sup>).

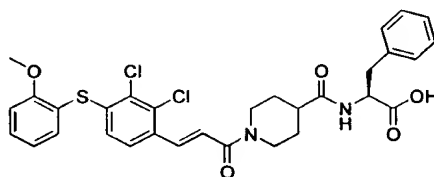
10

Example 388D(2-Methoxyphenyl)[3-chloro-6-hydroxy-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

15

The allyl group of Example 388C was removed as reported in the literature (Honda, M.; Morita, H.; Nagakura, I. J. Org. Chem. **1997**, 62, 8932.) and the carboxylic acid was converted to the amide as reported in Example 165 to provide the title compound as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.73 (d, *J*=16.3 Hz, 1H), 7.51 (d, *J*=7.4 Hz, 1H), 7.43 (d, *J*=7.4 Hz, 1H), 7.19 (d, *J*=7.9 Hz, 1H), 7.05

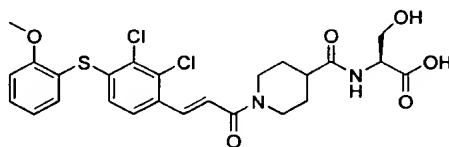
(dt,  $J=7.8$  Hz,  $J=1.1$  Hz, 1H), 6.70 (d,  $J=1.8$  Hz, 1H), 6.59 (d,  $J=6.59$  Hz, 1H), 4.30 (m, 1H), 3.95 (m, 2H), 3.80 (s, 3H), 2.85 (m, 2H), 1.87 (m, 2H), 1.45 (m, 2H). MS (APCI)  $m/z$  448 ( $M+H^+$ ).



### Example 389

(2-Methoxyphenyl) [2,3-dichloro-4-(E-(4-((1-(2-phenyl-1-carboxyethyl)amino)carbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

10 The methyl ester of the title compound was prepared by the procedure described in Example 363 using L-phenylalanine methyl ester as the coupling substrate. The methyl ester was then hydrolyzed as described in Example 340 to provide the title compound. HPLC (Supelco C-18 column, water:acetonitrile 100:0-0:100, 20 minute elution, flow rate 1.5 mL/min, RT = 13.97 min;  $^1H$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.45 (m, 2H), 1.56 (m, 1H), 1.68 (m, 1H), 2.41 (m, 1H), 2.71 (m, 1H), 2.83 (m, 2H), 3.08 (m, 2H), 3.79 (s, 3H), 4.12 (m, 1H), 4.30 (m, 1H), 4.41 (m, 1H), 6.55 (d, 1H), 7.09 (t, 1H), 7.22 (m, 6H), 7.48 (dd, 1H), 7.57 (m, 1H), 7.72 (d, 1H), 7.81 (d, 1H), 8.11 (m, 1H), 12.64 (br s, 1H); MS (ESI)  $m/e$  613 ( $M+H^+$ ).

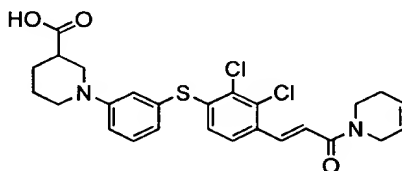


Example 390

(2-Methoxyphenyl) [2,3-dichloro-4-(E-(4-((1-(2-hydroxy-1-carboxyethyl)amino)carbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The methyl ester of the title compound was prepared by the procedure

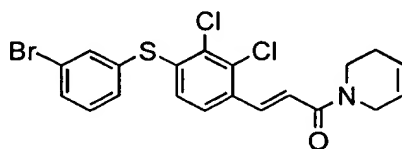
- 5 described in Example 363 using L-serine methyl ester as the coupling substrate. The methyl ester was then hydrolyzed as described in Example 340 to give the title compound. HPLC (Supelco C-18 column, water:acetonitrile 100:0- 0:100, 20 minute elution, flow rate 1.5 mL/min, RT = 11.79 min; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ
- 1.48 (m, 2H), 1.72 (m, 2H), 2.55 (m, 2H), 2.71 (m, 1H), 3.10 (m, 1H), 3.62 (m, 2H),
- 10 3.79 (s, 3H), 4.22 (m, 2H), 4.41 (m, 1H), 6.55 (d, 1H), 7.09 (t, 1H), 7.34 (m, 2H), 7.48 (m, 1H), 7.57 (m, 1H), 7.71 (d, 1H), 7.81 (d, 1H), 7.96 (br d, 1H); MS (ESI) *m/e* 553 (M+H)<sup>+</sup>.



15

Example 391

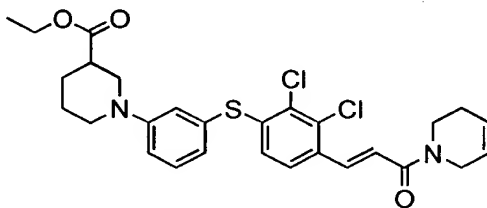
(3-(1-(3-Carboxypiperidinyl)phenyl)[2,3-dichloro-4-(E-(1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl]sulfide



Example 391A

(3-bromophenyl) [2,3-dichloro-4-(E-[(1,2,3,6-tetrahydropyridin-1-yl)carbonyl]ethenyl)phenyl]sulfide

Sub 119  
The title compound (1.2 g, 103%) was prepared from Example 384B (1.00 g, 2.48 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 1,2,3,6-tetrahydropyridine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.09-2.2 (m, 2H), 3.61-3.68 (m, 1H), 3.70-3.77 (m, 1H), 4.03 (m, 1H), 4.18 (m, 1H), 5.69-5.78 (m, 1H), 5.80-5.93 (m, 1H), 6.93 (d, J=9 Hz, 1H), 7.20-7.37 (m, 1H), 7.43-7.56 (m, 3H), 7.67-7.79 (m, 2H), 7.88-7.97 (m, 1H); MS (ESI) m/e 470, 472 (M+H)<sup>+</sup>.

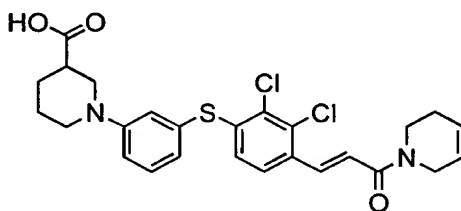
Example 391B

[3-(3-ethoxycarbonylpiperidine)] [2,3-dichloro-4-(E-[(1,2,3,6-tetrahydropyridin-1-yl)carbonyl]ethenyl)phenyl] sulfide

Sub 120  
The title compound (50 mg, 46%) was prepared by the procedures described in Example 384D, substituting morpholine with ethyl nipecotate. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.17 (t, J=6.8 Hz, 3H), 1.5-1.76 (m, 3H), 1.82-1.95 (m, 1H), 2.06-2.19 (m, 2H), 2.56-2.67 (m, 1H), 2.84-2.96 (m, 1H), 3.06-3.13 (m, 1H), 3.43-3.52 (m, 1H), 3.61-3.74 (m, 2H), 3.99-4.18 (m, 4H), 5.66-5.91 (m, 2H), 6.73 (d, J=9 Hz, 1H),

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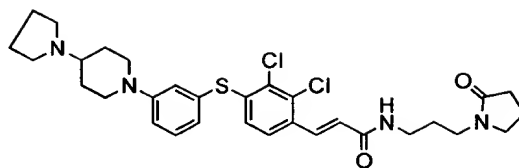
6.92 (d, J=7.5 Hz, 1H), 7.06-7.12 (m, 2H), 7.31-7.39 (m, 2H), 7.75 (d, J=15 Hz, 1H), 7.80-7.91 (m, 1H); MS (ESI)  $m/e$  545, 547 (M+H)<sup>+</sup>.

Example 391C

[3-(3-carboxypiperidine)] [2,3-dichloro-4-(E-[(1,2,3,6-tetrahydropyridine)-1-yl)carbonyl]ethenyl]phenyl] sulfide

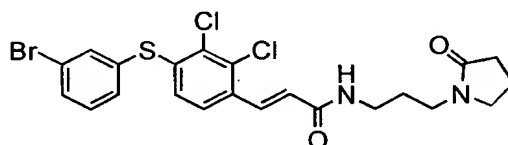
The title compound (20 mg, 49%) was prepared from Example 391B (43 mg, 0.08 mmol) using the procedures described in Example 340H. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500 MHz) δ 1.51-1.64 (m, 2H), 1.68-1.73 (m, 1H), 1.87-1.94 (m, 1H), 2.07-2.19 (m, 2H), 2.51-2.57 (m, 1H), 2.83-2.89 (m, 1H), 2.99-3.04 (m, 1H), 3.61-3.73 (m, 4H), 4.02 (br s, 1H), 4.15 (br s, 1H), 5.67-5.76 (m, 1H), 5.79-5.90 (m, 1H), 6.72 (d, J=7.5 Hz, 1H), 6.92 (J=6.25 Hz, 1H), 7.10-7.13 (m, 2H), 7.14-7.30 (m, 1H), 7.36 (t, J=7.5 Hz, 1H), 7.74 (d, J=15 Hz, 1H), 7.80-7.90 (m, 1H); MS (ESI)  $m/e$  517, 519 (M+H)<sup>+</sup>.

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Example 392

(3-(4-Pyrrolidin-1-yl)piperidin-1-yl)phenyl) [2,3-dichloro-4-(E-(((3-(2-pyrrolidinon-1-yl)propylamino)carbonyl)ethenyl)phenyl)sulfide

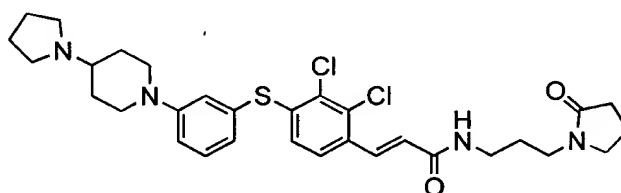
5

Example 392A

(3-bromophenyl) [2,3-dichloro-4-(E-(((3-(2-pyrrolidinon-1-yl)propylamino)carbonyl)ethenyl)phenyl)sulfide

10

The title compound (1.25 g, 95%) was prepared from Example 384B (1.00 g, 2.475 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 3-aminopropylpyrrolidine. MS (ESI)  $m/e$  529,  $(M+H)^+$ , 527,  $(M-H)^-$ .



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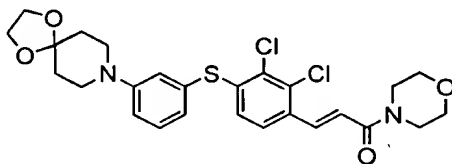
Example 392B

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(3-(4-Pyrrolidin-1-yl)piperidin-1-yl)phenyl [2,3-dichloro-4-(E-(((3-(2-pyrrolidinon-1-yl)propylamino)carbonyl)ethenyl)phenyl)sulfide

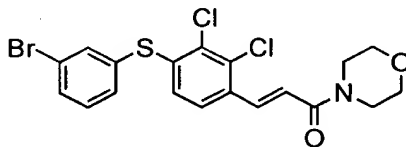
The title compound (32 mg, 27%) was prepared from Example 392A as described in Example 384D, substituting morpholine with 4-(1-

- 5 pyrrolidinyl)piperidine.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.60-1.67 (m, 4H), 1.84-2.90 (m, 5H), 2.91-2.03 (m, 1H), 2.04-2.11 (m, 3H), 2.20 (t,  $J=7.5$  Hz, 2H), 2.75 (br t,  $J=12.5$  Hz, 2H), 3.00-3.16 (m, XH), 3.21 (t,  $J=7.5$  Hz, XH), 3.33 (m, 1H), 3.46-3.64 (m, 1H), 3.87 (br d,  $J=10$  Hz, 2H), 6.59 (d,  $J=15$  Hz, 1H), 6.80 (d,  $J=8.75$  Hz, 1H), 6.94 (d,  $J=7.5$  Hz, 1H), 7.12-7.18 (m, 2H), 7.33 (t,  $J=7.5$  Hz, 1H), 7.57 (d,  $J=8.75$  Hz, 1H), 7.68 (d,  $J=15$  Hz, 1H), 8.24 (t,  $J=5$  Hz, 1H); MS (ESI)  $m/e$  601, 603,  $(M+H)^+$ ; 599, 601  $(M-H)^-$ .



Example 393

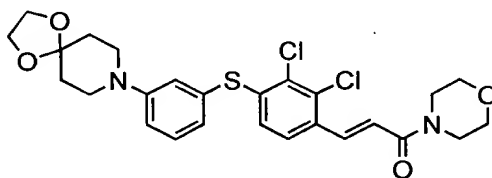
- 15 [3-(4-(Spiro-2,2-dioxolanyl)piperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl)sulfide



Example 393A

(3-bromophenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl] sulfide

The title compound (980 mg, 84%) was prepared from Example 384B (1.00 g, 2.48 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with morpholine. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) 3.53-3.63 (m, 6H), 3.68 (br s, 2H), 6.93 (d, J=8 Hz, 1H), 7.27 (d, J=15 Hz, 1H), 7.44-7.52 (m, 2H), 7.67-7.74 (m, 2H), 7.78 (d, J=15 Hz, 1H), 7.80 (d, J=8 Hz, 1H); MS (ESI) *m/e* 474 (M+H)<sup>+</sup>.



Example 393B

[3-(4-(Spiro-2,2-dioxolanyl)piperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl] sulfide

The title compound (32 mg, 27%) was prepared from Example 393A as described in Example 384D, substituting morpholine with 1,4-dioxo-8-azaspiro[4,5]decane. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 1.68 (t, J=5 Hz, 4H), 3.52-3.60 (m, 7H), 3.66 (br s, 2H), 3.91 (s, 4H), 6.71 (d, J=8.75 Hz, 1H), 6.91 (m, 1H), 7.11-7.13 (m, 2H), 7.22 (d, J=15 Hz, 1H), 7.35 (m, 1H), 7.76 (d, J=15 Hz, 1H), 7.85 (d, J=8.75 Hz, 1H); MS (ESI) *m/e* 535, 537 (M+H)<sup>+</sup>.

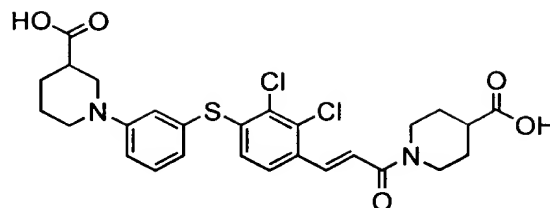
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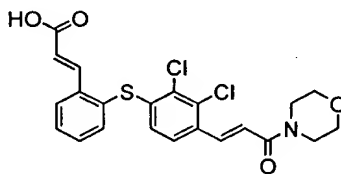
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Example 394

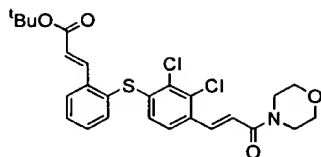
[3-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

5           The title compound (51 mg, 41%) was prepared from Example 384C as described in Example 384D, substituting morpholine with ethyl nipecotate followed by hydrolysis with LiOH as described in Example 340H. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.39-1.60 (m, 4H), 1.67-1.76 (m, 1H), 1.82-1.96 (m, 3H), 2.52-2.59 (m, 3H), 2.81-2.93 (m, 2H), 2.99-3.07 (m, 1H), 3.14-3.25 (m, 1H), 3.47-3.54 (m, 1H),  
10   3.69 (dd, J<sub>1</sub>=4 Hz, J<sub>2</sub>=12 Hz, 1H), 4.05-4.17 (m, 1H), 4.24-4.34 (m, 1H), 6.72 (d, J=8 Hz, 1H), 6.92 (d, J=8 Hz, 1H), 7.11 (m, 2H), 7.23 (d, J=15 Hz, 1H), 7.34-7.40 (m, 1H), 7.73 (d, J=15 Hz, 1H), 7.85 (d, J=8 Hz, 1H); MS (ESI) *m/e* 563, 565 (M+H)<sup>+</sup>.

Example 395

(2-(2-Carboxy)ethenyl)phenyl [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

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Example 395A

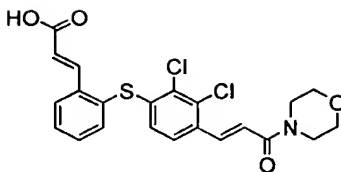
(2-(2-Tert-butyloxycarbonyl)ethenyl)phenyl [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl]sulfide

5 A solution of Example (2-bromophenyl) (50 mg, 0.11 mmol),  
 tris(benzylideneacetone)dipalladium[0] (5.1 mg, 0.0056 mmol), and tri-*o*-  
 tolylphosphine (11 mg, 0.035 mmol) in 0.2 mL DMF was degassed with nitrogen gas  
 for 10 min, then triethylamine (50  $\mu$ L, 36 mg, 0.36 mmol) and tert-butyl acrylate (50  
 10  $\mu$ L, 44 mg, 0.34 mmol) were added to the solution, and the vessel was sealed under  
 nitrogen and heated in a 100  $^{\circ}$ C oil bath for 17 h. The reaction was concentrated  
 under hi-vacuum, and the residue was partially purified by preparative TLC eluting  
 with 10% acetone-CH<sub>2</sub>Cl<sub>2</sub> to provide 42 mg (0.080 mmol, 73%) of the title compound  
 as a crude material. The compound was further purified by preparative HPLC (30-  
 100% MeCN in 0.1% aqueous TFA, 40 min elution, C-18 reverse-phase Sorbax 10  
 15 mm column, producing 26 mg (0.051 mmol, 47%) of the title compound as a glass.  
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.47 (s, 9H), 2.3-2.7 (v br s, 5H), 3.54-3.90 (2 br m,  
 8H), 6.32 (d, J=16 Hz, 1H), 6.46 (d, J=8 Hz, 1H), 6.69 (br d, J=15 Hz, 1H), 7.24 (br d,  
 partially overlapped with CHCl<sub>3</sub>, approx. 1H), 7.40-7.54 (m, 2H), 7.59 (dd, J=2,8 Hz,  
 1H), 7.75 (dd, J=2,8 Hz, 1H), 7.94 (br d, J=15 Hz, 1H), 7.98 (d, J=16 Hz, 1H); MS  
 20 (ESI) *m/e* 520, 522 (M+H)<sup>+</sup>.

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Example 395B

(2-(2-Carboxy)ethenyl)phenyl] [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

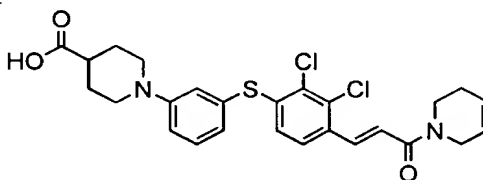
5

Example 395A (26 mg, 0.050 mmol) was dissolved in 1 mL

chloroform and 1 mL TFA and the solution was stirred at ambient temperature for 1 h.

The solvent was concentrated under reduced pressure to provide 25 mg (109%) of the title compound as an 85:15 mixture of *E*- and *Z*-cinnamide isomers. Data for major isomer: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.55-3.85 (2 br m, 9H), 6.42 (d, J=16 Hz, 1H), 6.47 (d, J=8 Hz, 1H), 6.69 (d, J=15 Hz, 1H), 7.24 (d, partially overlapped with CHCl<sub>3</sub>, approx. 1H), 7.43-7.56 (m, 2H), 7.78 (dd, J=2,8 Hz, 2H), 7.93 (d, J=15 Hz, 1H), 8.23 (d, J=16 Hz, 1H); MS (ESI) *m/e* 464, 466 (M+H)<sup>+</sup>.

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Example 396

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(1,2,3,6-tetrahydropyridine)-1-yl]carbonyl)ethenyl] sulfide

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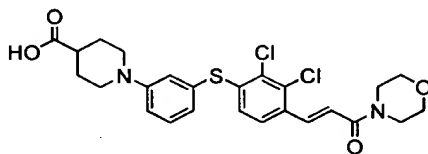
The title compound (22 mg, 58%) was prepared from Example 391A as described in Example 384D, substituting morpholine with ethyl isonipecotate

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followed by hydrolysis with LiOH as described in Example 340H.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.59-1.70 (m, 2H), 1.87-1.93 (m, 2H), 2.07-2.19 (m, 2H), 2.39-2.47 (m, 1H), 2.80-2.90 (m, 2H), 4.03 (br s, 1H), 4.16 (br s, 1H), 5.68-5.76 (m, 1H), 5.79-5.90 (m, 1H), 6.72 (d,  $J=8$  Hz, 1H), 6.93 (d,  $J=7$  Hz, 1H), 7.13 (m, 2H), 7.17-7.3 (m, 1H), 7.36 (t,  $J=7$  Hz, 1H), 7.75 (d,  $J=15$  Hz, 1H), 7.80-7.90 (m, 1H); MS (ESI)  $m/e$  517, 519 ( $M+H$ ) $^+$ .

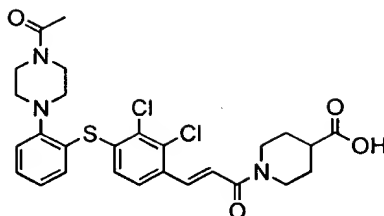


Example 397

[3-(4-Carboxypiperidinyl)phenyl] [2,3-dichloro-4-(E-[(4-morpholinyl)carbonyl]ethenyl)phenyl] sulfide

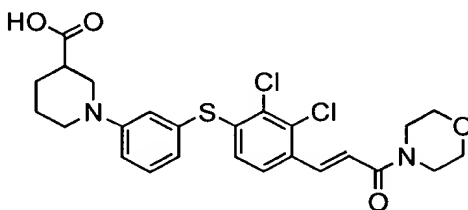
The title compound (39 mg, 79%) was prepared from Example 393A as described in Example 384D, substituting morpholine with ethyl isonipecotate followed by hydrolysis with LiOH as described in Example 340H.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.56-1.68 (m, 2H), 1.86-1.92 (m, 2H), 2.38-2.46 (m, 1H), 2.77-2.86 (m, 2H), 3.52-3.61 (m, 6H), 3.65-3.72 (m, 4H), 6.71 (d,  $J=8$  Hz, 1H), 6.91 (d,  $J=7$  Hz, 1H), 7.10 (m, 2H), 7.21 (d,  $J=15$  Hz, 1H), 7.34 (t,  $J=8$  Hz, 1H), 7.76 (d,  $J=15$  Hz, 1H), 7.83 (d,  $J=8$  Hz, 1H); MS (ESI)  $m/e$  521, 523 ( $M+H$ ) $^+$ .

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Example 398

[2-(4-Acetylpiperazin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-carboxypiperidin-1-yl)carbonyl]ethenyl)phenyl] sulfide

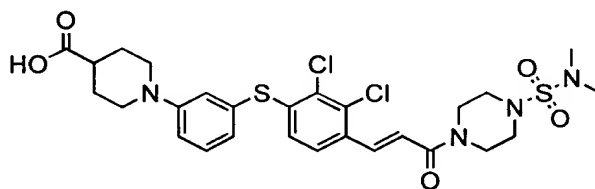
5 The title compound (19 mg, 83%) was prepared from Example 384C as described in Example 384D, substituting morpholine with 4-acetylpiperazine, followed by hydrolysis with LiOH as described in Example 340H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.38-1.54 (m, 2H), 1.82-11.92 (m, 2H), 2.00 (s, 3H), 2.51-2.60 (m, 1H), 2.87-3.00 (m, 5H), 3.13-3.27 (m, 1H), 3.36-3.46 (m, 4H), 4.06-4.18 (m, 1H),  
 10 4.22-4.36 (m, 1H), 6.91 (d, J=7.5 Hz, 1H), 7.10-7.17 (m, 1H), 7.20-7.25 (m, 2H), 7.28 (d, J=15 Hz, 1H), 7.39-7.45 (m, 1H), 7.77 (d, J=15 Hz, 1H), 7.89 (d, J=7.5 Hz, 1H); MS (ESI) *m/e* 562, 564 (M+H)<sup>+</sup>.

Example 399

[3-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-morpholinyl)carbonyl]ethenyl)phenyl] sulfide

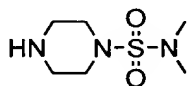
D01F1/95-03100

The title compound (30 mg, 60%) was prepared from Example 393A as described in Example 384D, substituting morpholine with ethyl nipecotate followed by hydrolysis with LiOH as described in Example 340H. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.51-1.60 (m, 1H), 1.66-1.72 (m, 1H), 1.87-1.94 (m, 1H), 2.79-2.87 (m, 1H), 2.96-3.02 (m, 1H), 3.44-3.72 (m, 12H), 6.71 (d, J=8 Hz, 1H), 6.90 (d, J=7 Hz, 1H), 7.09 (m, 2H), 7.21 (d, J=15 Hz, 1H), 7.32-7.38 (m, 1H), 7.76 (d, J=15 Hz, 1H), 7.84 (d, J=8 Hz, 1H); MS (ESI) *m/e* 521, 523 (M+H)<sup>+</sup>.



Example 400

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-(dimethylaminosulfamoyl)piperazin-1-yl)carbonyl]ethenyl)phenyl] sulfide



Example 400A

N,N-Dimethyl piperazinylsulfamide

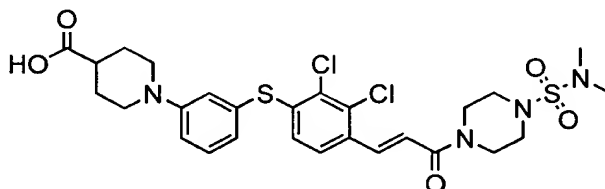
To a solution of *tert*-butyl 1-piperazinecarboxylate (2.5 g, 13.42 mmol) in tetrahydrofuran (21.5 ml, 0.25 M) at 0 °C was added triethylamine (2.25 mL, 16.11 mmol) followed by dimethylsulfamoyl chloride (1.73 mL, 16.11 mmol). The reaction

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mixture was stirred at 0 °C for 1 h, diluted with ethyl acetate (100 mL) and washed with saturated NaHCO<sub>3</sub> solution (2x30 mL), followed by brine (2x30 mL). The dried (Na<sub>2</sub>SO<sub>4</sub>) organic layer was evaporated to dryness under reduced pressure and the residue obtained was treated with 10% trifluoroacetic acid in methylene chloride (20 mL) at ambient temperature. After 48 h, methylene chloride was evaporated in vacuo to obtain a colorless syrup. This crude material was made basic (1 N NaOH, 50 mL), and the mixture was extracted sequentially with ethyl acetate (2x20 mL) and methylene chloride (2x30 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness under reduced pressure to obtain the title compound in quantitative yield. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.77 (s, 3H), 2.79 (s, 3H), 3.12-3.20 (m, 7H), 3.3 (m, 1H), 8.86 (br s, 1H); MS (ESI) *m/e* 194 (M+H)<sup>+</sup>.



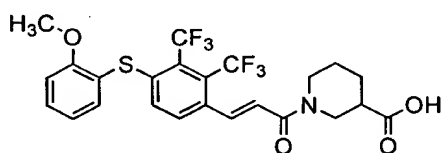
#### Example 400B

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(4-(dimethylaminosulfamoyl)piperazin-1-yl)carbonyl]ethenyl)phenyl] sulfide

The title compound was prepared from Example 384B as described in Example 340G, substituting methyl isonipecotate with Example 400A, followed by amination with ethyl isonipecotate as described in Example 396. <sup>1</sup>H NMR (500 MHz, MeOH-d<sub>4</sub>) δ 2.79-2.88 (m, 2H), 2.01-2.08 (m, 2H), 2.48-2.53 (m, 1H), 2.84 (s,

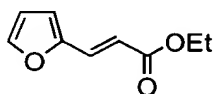
6H), 2.91-2.99 (m, 2H), 3.24-3.29 (m, 2H), 3.66-3.73 (m, 2H), 3.77 (m, 6H), 6.80 (d, J=7.5 Hz, 1H), 7.05(d, J=7.5 Hz, 1H), 7.11 (d, J=15 Hz, 1H), 7.16-7.22 (m, 2H), 7.39 (t, J=7.5 Hz, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.95 (d, J=15 Hz, 1H); MS (ESI) *m/e* 625, 627 (M-H)<sup>-</sup>.

5

Example 401

(2-Methoxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

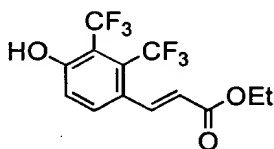
10

Example 401A

Ethyl 2-Furylacrylate

Ethyl iodide (64 mL, 0.796 mol) was added to furylacrylic acid (100 g, 0.724 mol), diisopropylethyl amine (140 mL, 0.796 mmol), in acetonitrile (1100 mL), and the mixture was heated to 60 °C. After 18 h, the dark solution was cooled to room temperature and concentrated in vacuo. The resulting brown sludge was diluted with Et<sub>2</sub>O (500 mL), washed with 1 N aqueous HCl (2x250 mL), washed with 0.2 N aqueous NaOH (2x250 mL), washed with saturated aqueous NaHCO<sub>3</sub> (1x250 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a black oil (114 g, 95%). <sup>1</sup>H NMR

(DMSO- $d_6$ , 300 MHz)  $\delta$  7.84 (d,  $J=1.7$  Hz, 1H), 7.46 (d,  $J=15.6$  Hz, 1H), 6.97 (d,  $J=3.4$  Hz, 1H), 6.33 (dd,  $J=3.4$  Hz,  $J=1.7$  Hz, 1H), 6.22 (d,  $J=15.9$  Hz, 1H), 4.17 (q,  $J=7.1$  Hz, 2H), 1.24 (t,  $J=7.1$  Hz, 3H); MS (APCI)  $m/z$  167 (M+H) $^+$ .



5

Example 401BEthyl E-2,3-bis(trifluoromethyl)-4-hydroxycinnamate

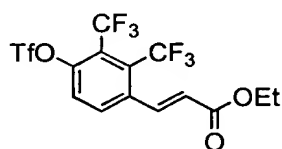
NOTE: "5627560"  
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A130

A solution of Example 401A (20 g, 0.12 mol) in tetrahydrofuran (40 mL) at -50 °C in a 600 mL Parr stirred reactor was treated with hexafluoroacetylene (24.4 g, 0.15 mol), the reactor sealed and heated to 110 °C for 22 hours, allowed to slowly cool to room temperature, and then concentrated to a brown oil (36 g). This oil was then treated with boron trifluoride etherate (33 mL, 0.275 mol) at room temperature for 17 hours, additional boron trifluoride etherate (16 mL, 0.135 mol) added, stirred six hours, cooled to 0 °C, diethyl ether (200 mL) added, followed by slow addition of 150 mL of 2M potassium carbonate (vigorous gas evolution). This mixture was diluted with additional diethyl ether, layers separated, organic layer washed with brine, dried (MgSO<sub>4</sub>) and concentrated to give 39 grams of a brown semi-solid. This semi-solid was diluted with 75 mL of dichloromethane and then flash chromatographed on silica gel with 10-50% ethyl acetate/hexane to provide the title compound (22.8 g, 58%). mp 138-140 °C;  $^1\text{H}$  NMR (300 MHz,  $d_6$  DMSO)  $\delta$  11.64 (bs, 1H), 7.95 (d, 1H), 7.78 (dq, 1H), 7.33 (d, 1H), 6.47 (d, 1H), 4.21 (q, 2H), 1.26 (t,

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130

3H); MS (APCI-NH<sub>3</sub>) m/e 329 (M+H)<sup>+</sup>, 346 (M+NH<sub>4</sub>)<sup>+</sup>, 327 (M-H)<sup>-</sup>. Analytical HPLC: 4.6X250 mm Zorbax C18 column, 1.5 mL/min, 254 nm, CH<sub>3</sub>CN:H<sub>2</sub>O with 0.1% TFA, 0:100 ramp to 90:10 (0-10 min), 90:10 (10-18 min), ramp to 0:100 (18-20 min), Rt = 10.6 min (98.3 area%).

5

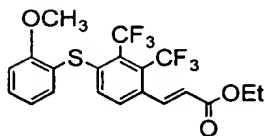
Example 401CEthyl E-4-(trifluoromethanesulfonyl)-2,3-bis(trifluoromethyl)cinnamate

NOTE: 55274560

10 Triflic anhydride (670  $\mu$ L, 3.97 mmol) was added to a mixture of Example 401B (1.00 g, 3.05 mmol) and pyridine (6.5 mL). After 2 h, the dark solution was diluted with Et<sub>2</sub>O (75 mL), washed with 1 N aqueous HCl (2x50 mL), washed with saturated aqueous NaHCO<sub>3</sub> (1x75 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a dark amber oil (1.35 g, 96%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  8.33 (d, *J*=8.8 Hz, 1H), 8.11 (d, *J*=8.8 Hz, 1H), 7.87-7.78 (m, 1H), 6.67 (d, *J*=16.0 Hz, 1H), 4.24 (q, *J*=7.1 Hz, 2H), 1.27 (t, *J*=7.1 Hz, 3H); MS (APCI) *m/z* 478 (M+NH<sub>4</sub>)<sup>+</sup>, 495 (M+Cl)<sup>-</sup>.

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131

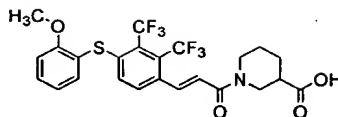
Example 401D

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-  
(ethoxycarbonyl)ethenyl]phenyl]sulfide

5 2-Methoxythiophenol (524  $\mu$ L, 4.30 mmol) was added to Example 401C (1.69  
g, 3.90 mmol), cesium carbonate (3.18 g, 9.75 mmol), and DMF (8 mL). After 15h,  
the dark solution was diluted with Et<sub>2</sub>O (100 mL), washed with water (1x50 mL),  
washed with 1 N aqueous HCl (2x100 mL), washed with saturated aqueous NaHCO<sub>3</sub>  
(1x100 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a dark oil. Flash silica gel  
10 column chromatography (85:15 hexane:ethyl acetate) provided the ethyl ester (1.16 g,  
66%) as a yellow oil. The ester (858 mg) was subsequently hydrolyzed as previously  
detailed in Example 155 to provide the title compound (670 mg, 84%) as a white  
solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  7.89 (d,  $J=8.8$  Hz, 1H), 7.74-7.67 (m, 1H),  
7.55 (dd,  $J=7.5$  Hz,  $J=1.7$  Hz, 1H), 7.50 (dd,  $J=9.9$  Hz,  $J=1.7$  Hz, 1H), 7.20 (d,  $J=8.4$   
15 Hz, 1H), 7.19 (t,  $J=7.1$  Hz, 1H), 7.07 (dt,  $J=7.5$  Hz,  $J=1.3$  Hz, 1H), 6.44 (d,  $J=15.6$   
Hz, 1H), 3.75 (s, 3H). MS (APCI)  $m/z$  421 (M-H<sup>+</sup>).

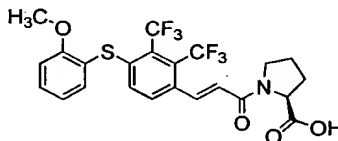
0954195-033100

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Example 401E

(2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((3-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

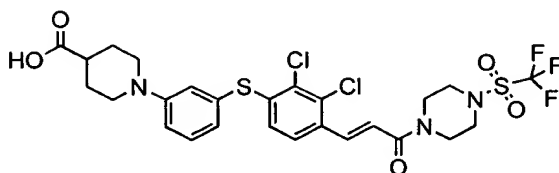
- 5        Example 401D was processed as detailed in Examples 137 and 155 to provide the title compound (168 mg, 86%) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.95 (d, 1H), 7.57 (m, 1H), 7.50 (t, 1H), 7.46 (d, 1H), 7.20 (d, 1H), 7.15 (d, 1H), 7.14 (d, 1H), 7.06 (t, 1H), 4.4 (m, 1H), 4.01 (m, 2H), 3.75 (s, 3H), 1.93 (m, 2H), 1.63 (m, 2H), 1.42 (m, 2H). MS (APCI) *m/z* 534 (M+H<sup>+</sup>). Anal. calcd for
- 10    C<sub>24</sub>H<sub>21</sub>F<sub>6</sub>NO<sub>4</sub>S+0.75M H<sub>2</sub>O: C, 52.70; H, 4.15; N, 2.56. Found: C, 53.01; H, 3.78; N, 2.17.

Example 402

- 15    (2-Methoxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((2-carboxypyrrolidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

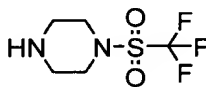
- Example 401D was processed as reported in Example 401E, substituting L-proline methyl ester hydrochloride for the amine. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.98 (d, *J*=8.2 Hz, 1H), 7.64 (m, 1H), 7.53 (d, *J*=8.2 Hz, 1H), 7.50 (t, *J*=7.4 Hz, 1H),
- 20    7.21 (d, 1H), 7.19 (d, 1H), 7.07 (t, *J*=7.8 Hz, 1H), 6.95 (d, *J*=15.0 Hz, 1H), 4.34 (m,

1H), 3.70 (m, 2H), 3.76 (s, 3H), 2.08 (m, 2H), 1.91 (m, 2H); MS (APCI)  $m/z$  520 (M+H<sup>+</sup>). Anal. calcd for C<sub>23</sub>H<sub>19</sub>F<sub>6</sub>NO<sub>4</sub>S: C, 53.18; H, 3.69; N, 2.70. Found: C, 52.88; H, 3.86; N, 2.43.



### Example 403

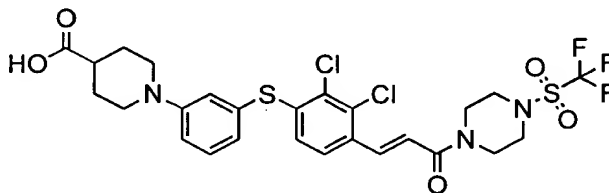
[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-((trifluoromethylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide



### Example 403A

#### Piperazine-1-trifluoromethylsulfonyl derivative

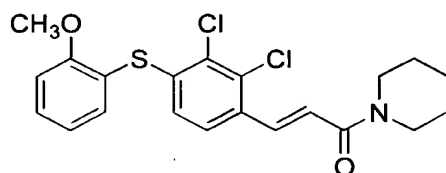
The title compound (1.65 g, 72%) was prepared as described in Example 400A, substituting dimethylsulfamoyl chloride with trifluoromethanesulfonyl chloride (1.26 ml, 11.81 mmol). MS (ESI)  $m/e$  219 (M+H)<sup>+</sup>.



### Example 403B

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(*E*-((4-  
((trifluoromethylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

Example 403B (51 mg, 38%) was prepared from Example 384B as described in Example 340G, substituting methyl isonipecotate with Example 403A followed by amination with ethyl isonipecotate as described in Example 396. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 1.56-1.66 (m, 2H), 2.84-2.91 (m, 2H), 2.37-2.45 (m, 1H), 2.77-2.86 (m, 2H), 3.63-3.70 (m, 7H), 3.72-3.85 (m, 3H), 6.72 (d, J=8.75 Hz, 1H), 6.90 (d, J=7.5 Hz, 1H), 7.09 (m, 1H), 7.11 (s, 1H), 7.21 (d, J=15 Hz, 1H), 7.34 (t, J=7.5 Hz, 1H), 7.76 (d, J=15 Hz, 1H), 7.81 (d, J=8.75 Hz, 1H); MS (ESI) *m/e* 650, 652 (M-H).

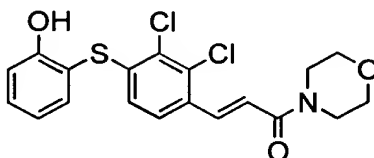


Example 404

(2-Methoxyphenyl)[2,3-dichloro-4-(*E*-(piperidin-1-ylcarbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-(*E*-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with piperidine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.48 (m, 4H), 1.59 (m, 2H), 3.55 (m, 4H), 3.79 (s, 3H), 6.55 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 6.0 Hz, 1H), 7.25 (s, 1H), 7.48 (dd, J = 7.8, 1.7 Hz, 1H), 7.56 (m, 1H), 7.72 (d, J = 15.6 Hz, 1H), 7.82

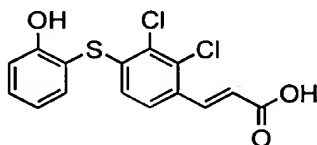
(d,  $J = 8.5$  Hz, 1H); MS (ESI<sup>+</sup>)  $m/z$  422, 424 (M+H)<sup>+</sup>. Anal. calcd for C<sub>21</sub>H<sub>21</sub>NCl<sub>2</sub>SO<sub>2</sub>: C, 59.72; H, 5.01; N, 3.32. Found: C, 59.52; H, 4.94; N, 3.05.



5

Example 405

(2-Hydroxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide



10

Example 405A

(2-Hydroxyphenyl) [2,3-dichloro-4-(E-(carboxy)ethenyl)phenyl]sulfide

Boron tribromide (84 mL of a 1.0M solution in CH<sub>2</sub>Cl<sub>2</sub>) was added to a suspension of Example 310C in CH<sub>2</sub>Cl<sub>2</sub> (85 mL) at 0 °C. After addition was completed, the ice-water bath was removed, and the homogeneous dark solution was stirred for 2h before the mixture was poured into 1 N aqueous HCl (100 mL) and ice (100 g), and extracted with EtOAc (3x100 mL). The organic layers were combined, washed with brine (1x50 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a white solid (11.3 g). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  10.26 (s, 1H), 7.82 (d,  $J=15.6$ , 1H), 7.74 (d,  $J=8.5$  Hz, 1H), 7.44 (dt,  $J=7.8$  Hz,  $J=1.7$  Hz, 1H), 7.41 (dd,  $J=7.4$  Hz,  $J=1.7$

A  
133

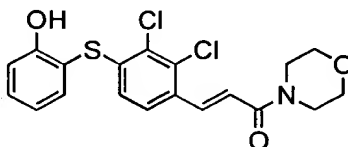
15

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360

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133

Hz, 1H), 7.05 (dd,  $J=8.4$  Hz,  $J=1.3$  Hz, 1H), 6.94 (dt,  $J=7.8$  Hz,  $J=1.4$  Hz, 1H), 6.52 (d,  $J=8.2$  Hz, 1H), 6.50 (d,  $J=16.0$  Hz, 1H); MS (APCI)  $m/z$  339 (M-H)<sup>-</sup>, 375 (M+Cl)<sup>-</sup>.



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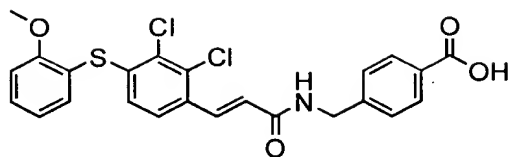
Example 405B

(2-Hydroxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

Example 405A (11.3 g) was processed as reported in Example 310D to provide the title product (8.47 g, 62%) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 10.24 (s, 1H), 7.81 (d,  $J=8.9$ , 1H), 7.77 (d,  $J=14.9$  Hz, 1H), 7.44 (dt,  $J=6.4$  Hz,  $J=1.7$  Hz, 1H), 7.39 (dd,  $J=8.2$  Hz,  $J=1.7$  Hz, 1H), 7.05 (dd,  $J=8.1$  Hz,  $J=1.0$  Hz, 1H), 6.94 (dt,  $J=7.8$  Hz,  $J=1.0$  Hz, 1H), 6.52 (d,  $J=8.8$  Hz, 1H), 6.53 (d,  $J=8.8$  Hz, 1H); MS (APCI)  $m/z$  410 (M+H)<sup>+</sup>, 446 (M+Cl)<sup>-</sup>.

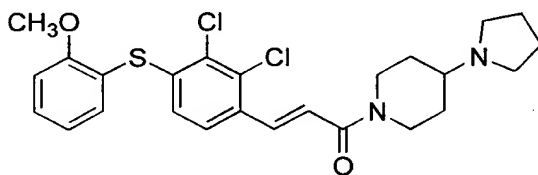
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007EE0" 5627560

361

Example 406

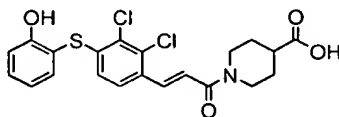
(2-Methoxyphenyl) [2,3-dichloro-4-(E-(((4-carboxyphenyl)methyl)amino)carbonyl)ethenyl]phenyl]sulfide

- 5 The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-( E-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with methyl 4-(aminomethyl)benzoate hydrochloride following by hydrolysis. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) 83.79 (s, 3H), 4.46 (s, 2H), 6.60 (d, J = 8.1 Hz, 1H), 6.66 (d, J = 15.6 Hz, 1H), 7.08 (t, J = 8.4 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.51 (m, 3H), 7.75 (d, J = 15.6 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 8.83 (t, J = 5.7 Hz, 1H), 12.90 (brs, 1H); MS (ESI<sup>+</sup>) *m/z* 488,490 (M+H)<sup>+</sup>. Anal. calcd for C<sub>24</sub>H<sub>19</sub>NCl<sub>2</sub>O<sub>4</sub>S: C, 59.02; H, 3.92; N, 2.87. Found: C, 58.97; H, 4.07; N, 2.71.


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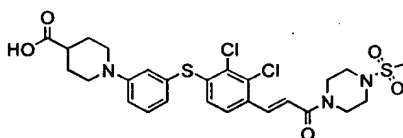
Example 407(2-Methoxyphenyl) [2,3-dichloro-4-(E-(((4-pyrrolidin-1-yl)piperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared by the procedures described in Example 1C substituting Example 1B with (2-methoxy) [2,3-dichloro-4-( E-(2-carboxyethenyl)phenyl] sulfide and substituting 6-amino-1-hexanol with 4-(pyrrolidinyl)piperidine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.48 (m, 2H), 1.84 (m, 2H), 2.00 (m, 2H), 2.10 (m, 2H), 2.65 (m, 1H), 3.10 (m, 3H), 3.35 (m, 1H), 3.50 (m, 1H), 3.80 (s, 3H), 4.38 (m, 2H), 4.52 (m, 1H), 6.56 (d, J = 8.5 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.26 (d, J = 15.2 Hz, 1H), 7.48 (dd, J = 7.8, 1.7 Hz, 1H), 7.57 (t, J = 8.2 Hz, 1H), 7.76 (d, J = 15.3 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H); MS (ESI<sup>+</sup>) *m/z* 491, 493 (M+H)<sup>+</sup>. Anal. calcd for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>Cl<sub>2</sub>O<sub>2</sub>S 1.8 TFA: C, 49.30; H, 4.31; N, 4.02. Found: C, 49.08; H, 4.31; N, 3.97.

Example 408(2-Hydroxyphenyl)[2,3-dichloro-4-(E-((4-carboxypiperidin-1-yl)carbonyl)ethenyl)phenyl]sulfide

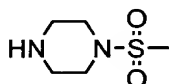
Example 405A (119 mg) was processed as detailed in Example 165 to provide the title compound as a white solid (43 mg, 28%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 10.23 (s, 1H), 7.81 (d, J=8.8, 1H), 7.72 (d, J=15.2 Hz, 1H), 7.42 (dt, J=7.8 Hz, J=1.7

Hz, 1H), 7.39 (dd,  $J=7.1$  Hz,  $J=1.7$  Hz, 1H), 7.21 (d,  $J=15.3$  Hz, 1H), 7.05 (dd,  $J=8.2$  Hz,  $J=1.0$  Hz, 1H), 6.93 (dt,  $J=7.4$  Hz,  $J=1.0$  Hz, 1H), 6.53 (d,  $J=8.5$  Hz, 1H), 4.25 (m, 1H), 4.03 (m, 2H), 2.85 (m, 2H), 1.87 (m, 2H), 1.44 (m, 2H). MS (APCI)  $m/z$  452 ( $M+H^+$ ), 450 ( $M-H^+$ ), 486 ( $M+Cl$ ). Anal. calcd for  $C_{21}H_{19}Cl_2NO_4S+0.25M H_2O$ : C, 55.21; H, 4.30; N, 3.07. Found: C, 55.26; H, 4.29; N, 2.72.



#### Example 409

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-((methylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

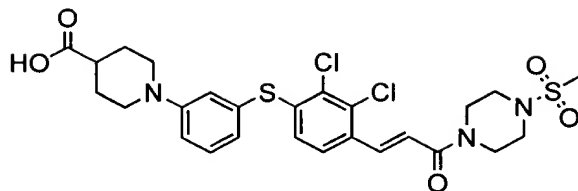


#### Example 409A

#### Piperazine methylsulfonamide

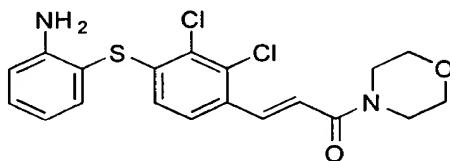
The title compound (1.65 g, 72%) was prepared as described in Example 400A, substituting dimethylsulfamoyl chloride with methanesulfonyl chloride (1.26 ml, 11.81 mmol).

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Example 409B

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-  
((methylsulfonyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

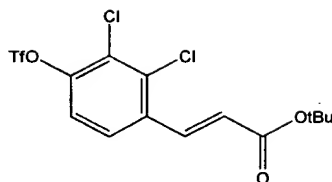
5 Example 409B (48 mg, 72%) was prepared from Example 384B as described  
in Example 340G, substituting methyl isonipecotatate with Example 409A followed by  
amination with ethyl isonipecotatate as described in Example 396. <sup>1</sup>H NMR (300  
MHz, DMSO-d<sub>6</sub>) δ 1.55-1.71 (m, 2H), 1.83-1.94 (m, 2H), 2.36-2.48 (m, 1H), 2.77-  
2.86 (m, 2H), 2.88 (s, 3H), 3.10-3.18 (m, 4H), 3.66-3.84 (m, 6H), 6.73 (d, J=8 Hz,  
10 1H), 6.93 (d, J=7.5 Hz, 1H), 7.11 (m, 1H), 7.13 (s, 1H), 7.25 (d, J=15 Hz, 1H), 7.32-  
7.41 (m, 1H), 7.78 (d, J=15 Hz, 1H), 7.85 (d, J=8 Hz, 1H); MS (ESI) *m/e* 598, 600  
(M+H)<sup>+</sup>; 596, 598 (M-H)<sup>-</sup>.

Example 410

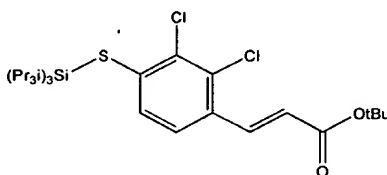
(2-Aminophenyl) [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl]  
sulfide

0954195-033100

365

Example 410Atert-Butyl 2,3-dichloro-4-((trifluoromethyl)sulfonyloxy)cinnamate

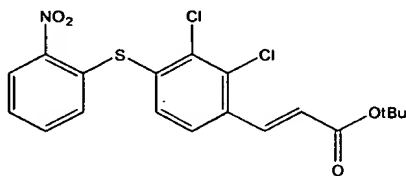
Sub A 135  
The title compound was constructed according to the procedure for Example 340D and 340E, except using *tert*-butyl acrylate instead of methyl acrylate. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.11 (d, 1H), 7.78 (d, 1H), 7.72 (d, 1H), 6.72 (d, 1H), 1.5 (s, 9H); MS (APCI-NH<sub>3</sub>) *m/e* 456 (M+Cl)<sup>-</sup>.

Example 410Btert-Butyl 2,3-dichloro-4-((triisopropylsilyl)thio)cinnamate

Sub A 136  
Sodium hydride (3.05 g of 60% dispersion, 76 mmol) that had been rinsed with dry tetrahydrofuran (2x), was suspended in 128 mL of THF, cooled to -5 °C, and slowly treated with triisopropylsilyl thiol (12.2 mL, 57 mmol), maintaining an internal temperature below 4 °C, stirred at 0 °C for 1.5 h, then added to a second flask containing Example 410A (20 g, 47.4 mmol) and tetrakis(triphenyl)phosphine palladium (4.4 g, 3.8 mmol) in 95 mL of THF. The reaction was heated at reflux for 8 h, then allowed to cool to ambient temperature and concentrated. The resultant slurry

Sub  
A136  
was diluted with ethyl acetate, filtered through celite, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The resultant black residue was flash chromatographed on silica gel with 2.5-5% acetone/hexane to provide the title compound (18.2 g, 83%).

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.82 (d, 1H), 7.78 (d, 1H), 7.0 (d, 1H), 6.5 (d, 1H),  
5 1.5 (s, 9H), 1.35 (m, 3H), 1.09 (d, 18H); MS (APCI-NH<sub>3</sub>) *m/e* 462 (M+H)<sup>+</sup>.

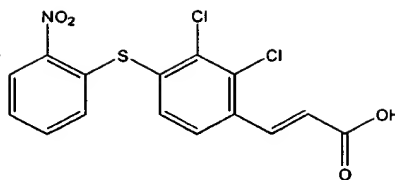


#### Example 410C

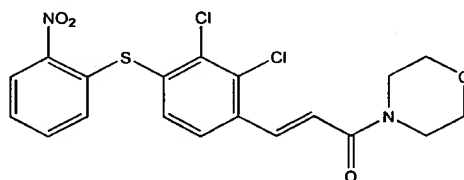
##### (2-Nitrophenyl) [2,3-dichloro-4-(E-((tert-butyloxycarbonyl)ethenyl)phenyl] sulfide

- 10 A solution of Example 410B in toluene (40 mL) was treated with cesium fluoride (600 mg, 4 mmol) followed by 2-fluoronitrobenzene (5.03 mL, 47.4 mmol), then heated at reflux for 2 h, then allowed to cool and the mixture was concentrated under reduced pressure. The resultant dark brown slurry was diluted with ethyl acetate, washed with water (2x), 1 M NaOH, (2x), water (2x), dried (Na<sub>2</sub>SO<sub>4</sub>) and
- 15 concentrated. The 21.2 grams of crude product was flash chromatographed on silica gel with 10% acetone/hexane to provide the title compound (8.92 g, 53%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 8.17 (dd, 1H), 7.95 (d, 1H), 7.83 (d, 1H), 7.78 (m, 1H), 7.48 (m, 1H), 7.3 (dd, 1H), 7.17 (d, 1H), 6.6 (d, 1H), 1.5 (s, 3H); MS (APCI-NH<sub>3</sub>) *m/e* 427 (M+H)<sup>+</sup>.

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Example 410D(2-Nitrophenyl) [2,3-dichloro-4-(E-((carboxy)ethenyl)phenyl] sulfide

A solution of Example 410C (3.2 g, 7.5 mmol) in dichloromethane (12 mL) at  
 5 room temperature was treated with trifluoroacetic acid (4 mL), stirred 30 minutes, and  
 concentrated to give the title compound (2.8 g, 100%) as an off-white solid. <sup>1</sup>H NMR  
 (300 MHz, DMSO-d<sub>6</sub>) δ 8.16 (dd, 1H), 7.94 (d, 1H), 7.86 (d, 1H), 7.76 (m, 1H), 7.48  
 (m, 1H), 7.29 (dd, 1H), 7.11 (d, 1H), 6.61 (d, 1H); MS (APCI-NH<sub>3</sub>) *m/e* 371 (M+H)<sup>+</sup>.



10

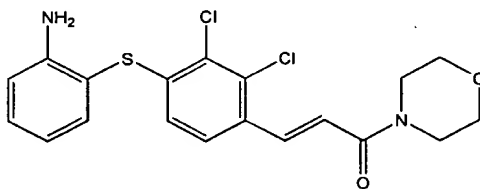
Example 410E(2-Nitrophenyl) [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

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A137  
 A solution of Example 410D (2.7 g, 7.29 mmol) in dimethylformamide (32  
 mL) was treated with hydroxybenzotriazole hydrate (1.2 g, 8.0 mmol), morpholine  
 15 (1.4 mL, 16 mmol) and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide  
 hydrochloride (1.53 g, 8.0 mmol), stirred at room temperature for 64 hours. The  
 heterogeneous mixture was filtered, the white solid washed with water, and then dried  
 in a vacuum oven at 50 °C for 24 hours to provide 2.8 g (88%) of the title compound

Sub  
A 137

368

as a white powder. mp 210-213 °C; <sup>1</sup>H NMR (300 MHz, d6 DMSO) δ 8.15 (dd, 1H), 8.03(d, 1H), 7.82 (d, 1H), 7.74 (m, 1H), 7.45 (m, 1H), 7.32 (d, 1H), 7.2 (m, 2H), 3.7 (m, 2H), 3.6 (m, 6H); MS (APCI-NH<sub>3</sub>) m/e 440 (M+H)<sup>+</sup>.



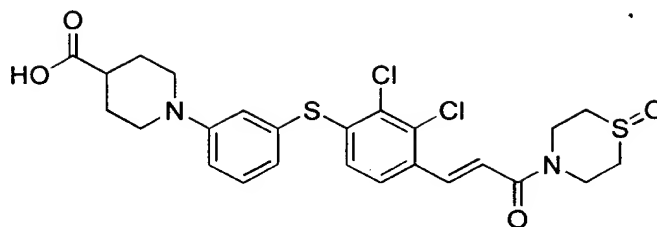
5

Example 410F

(2-Aminophenyl) [2,3-dichloro-4-(E-((4-morpholinyl)carbonyl)ethenyl)phenyl]  
sulfide

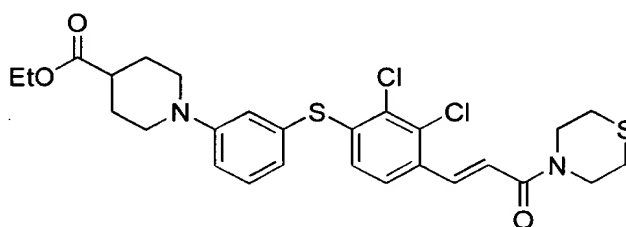
A solution of iron powder (1.3 g, 22.8 mmol) and ammonium chloride (292 mg, 5.46 mmol) in ethanol (9 mL) and distilled water (9 mL) at 105 °C was treated with example 410F (2 g, 4.55 mmol) in ethanol (20 mL), stirred for one hour and then allowed to cool to room temperature. The resultant heterogeneous black mixture was filtered through a plug of Celite, rinsed through with ethyl acetate (100 mL), the filtrate washed with 1 M potassium carbonate, brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give 1.9 g (100%) of the title compound as an off-white powder. mp 230-240 °C (dec); <sup>1</sup>H NMR (300 MHz, d6 DMSO) δ 7.9 (d, 1H), 7.8 (d, 1H), 7.2 (d, 1H), 6.95 (dt, 1H), 6.84 (m, 2H), 6.68 (d, 1H), 6.58 (dt, 1H), 5.05 (bs, 2H), 3.7 (m, 2H), 3.6 (m, 6H); MS (APCI-NH<sub>3</sub>) m/e 410 (M+H)<sup>+</sup>; Analytical HPLC: 4.6X250 mm Zorbax C18 column, 1.5 mL/min, 254 nm, CH<sub>3</sub>CN:H<sub>2</sub>O with 0.1% TFA, 0:100 ramp to 90:10 (0-10 min), 90:10 (10-18 min), ramp to 0:100 (18-20 min), Rt = 9.2 min.

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Example 411

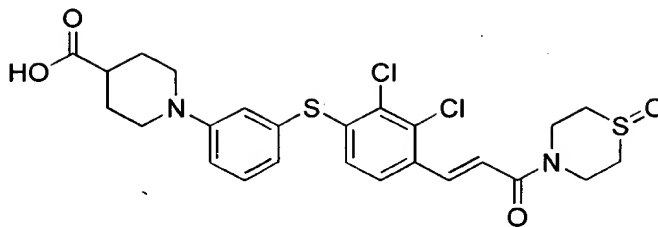
(3-(4-carboxypiperidin-1-yl)phenyl)[2,3-dichloro-4-(E-((S-oxothiophorin-1-yl)carbonyl)ethenyl)phenyl] sulfide



Example 411A

[3-(4-Ethoxycarbonyl)piperidin-1-yl] [2,3-dichloro-4-(E-(thiomorpholin-ylcarbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 397B substituting morpholine with thiomorpholine. MS (APCI<sup>+</sup>) *m/z* 565, 567 (M+H)<sup>+</sup>.

Example 411B

(3-(4-carboxypiperidin-1-yl)phenyl)[2,3-dichloro-4-(E-((S-oxothiophosphorin-1-yl)carbonyl)ethenyl)phenyl] sulfide

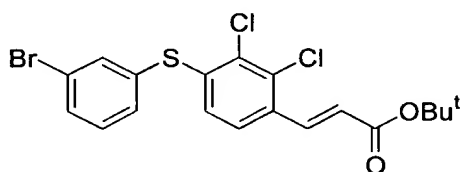
- 5 To a solution of Example 411A (107 mg, 0.189 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) was added mCPBA (80%, 41 mg, 0.189 mmol) at 0 °C. After stirring at the same temperature for 2 h, THF (2 mL) was added. The solution was concentrated to 1 mL, and was diluted with THF to 3 mL. Lithium hydroxide monohydrate (24 mg) in water (1 mL) was then added. The mixture was stirred at room temperature for 3 hours.
- 10 The formed transparent solution was separated by HPLC (Zorbax C-18) to give the title compound (68 mg). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.64 (m, 2H), 1.90 (m, 2H), 2.41 (m, 1H), 2.86 (m, 4H), 3.62 (m, 2H), 3.95 (m, 1H), 4.18 (m, 1H), 4.3 (m, 4H), 6.71 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.13 (s, 1H), 7.28 (d, J = 15.3 Hz, 1H), 7.36 (t, J = 8.8 Hz, 1H), 7.80 (d, J = 15.3 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H); MS (APCI<sup>+</sup>) m/z 553,555 (M+H)<sup>+</sup>. Anal. calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>Cl<sub>2</sub>S<sub>2</sub>O<sub>4</sub> 2 TFA: C, 44.57; H, 3.61; N, 3.58. Found: C, 44.34; H, 3.76; N, 3.51.

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O=C(O)C1CCN(C1)c2ccc(Sc3cc(Cl)c(Cl)cc3/C=C/C(=O)N4CC(O)CC4)cc2

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide



(3-Bromophenyl) [2,3-dichloro-4-(*E*-((*tert*-butyloxycarbonyl)ethenyl)phenyl] sulfide

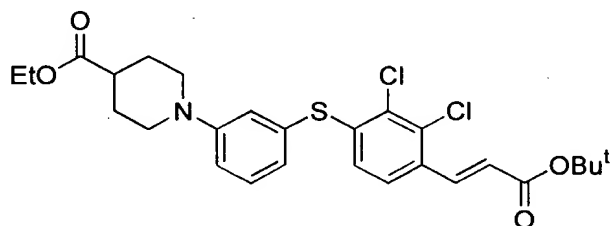
To a solution of Example 384B (2.35 g, 5.82 mmol) in THF (23 mL) at 5 °C was added *tert*-butyl trichloroacetimidate (2.6 mL, 14.54 mmol) and boron trifluoride-etherate (2.35 mL, 18.54 mmol). The solution was stirred at the same temperature for 10 minutes, and was then warmed up to room temperature for 5 h. The yellow solution was poured into aq. NaHCO<sub>3</sub> solution, and the mixture was extracted with ethyl acetate. The combined organic phases were washed with water, dried over anhydrous MgSO<sub>4</sub>, and concentrated. The residual white solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and was precipitated by adding hexane. The formed suspension was filtered through silica gel, and washed with 1:8 EtOAc/hexane. The solution was concentrated and was further purified by flash chromatography (silica gel, 1:20

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A 139

EtOAc/hexane) to give the title compound (2.50 g, 94%). MS (APCI<sup>+</sup>) *m/z* 461 (M+H)<sup>+</sup>.



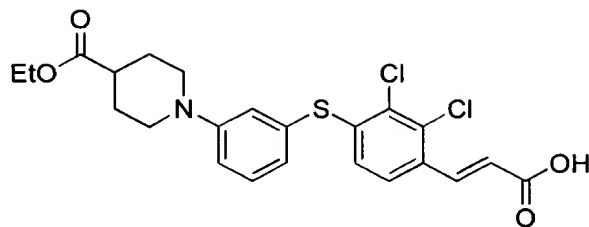
5

Example 412B

(3-(4-carboethoxypiperidin-1-yl)phenyl)[2,3-dichloro-4-( E-(carbo-t-  
butoxyethenyl)phenyl] sulfide

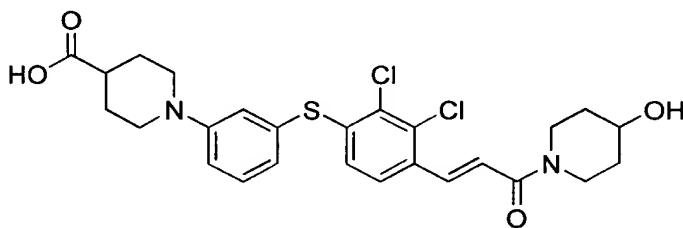
0541795-03100  
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A pressure tube was charged with Example 412A (589 mg, 1.28 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (30 mg, 0.032 mmol), 2-dicyclohexylphosphanyl-2'-dimethylaminobiphenyl (26 mg, 0.064 mmol), and anhydrous K<sub>3</sub>PO<sub>4</sub> (382 mg, 1.8 mmol), and was purged with nitrogen. DME (4 mL) and ethyl isonipecotate (242 mg, 1.54 mmol) were added via syringe, and the mixture was purged with nitrogen again. The red reaction mixture was stirred at room temperature for 0.5 h and at 95 °C for 15 h. After the reaction mixture was cooled, the it was diluted with ethyl acetate, and washed with brine. The aqueous phase was extracted with ethyl acetate. The combined ethyl acetate solution was concentrated and the residual oil was separated by flash chromatography (silica gel, 1:6 EtOAc/hexane) to give the title compound (523 mg, 76%). MS (APCI<sup>+</sup>) *m/z* 536 (M+H)<sup>+</sup>.

Example 412C

[3-(4-(Ethoxycarbonyl)piperidin-1-yl)phenyl] [2,3-dichloro-4-(E-(carboxy)ethenyl)phenyl] sulfide

- 5 To a solution of Example 412B (510 mg, 0.95 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) at  $0^\circ\text{C}$  was added trifluoroacetic acid (1.6 mL). The yellow solution was stirred at  $0^\circ\text{C}$  for 1 h, and was warmed to room temperature for 3 h. After diluting with  $\text{CH}_2\text{Cl}_2$ , the solution was poured into aq.  $\text{NaHCO}_3$  solution. The inorganic phase was acidified to pH 5, and was extracted with 10% MeOH in  $\text{CH}_2\text{Cl}_2$ . The combined organic phases
- 10 were washed with water, concentrated under vacuum and dried to give the title compound (472 mg, 100%). MS (APCI<sup>+</sup>)  $m/z$  480 ( $\text{M}+\text{H}$ )<sup>+</sup>.

Example 412D

- 15 [3-(4-carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

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A141

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142

To a suspension of Example 412C (150 mg, 0.31 mmol) in DMF (3 mL) was added 4-hydroxypiperidine (63 mg, 0.62 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (120 mg, 0.62 mmol), HOBt (84 mg, 0.62 mmol) and triethylamine (87  $\mu$ L, 0.62 mmol) at room temperature. The mixture was stirred at the same

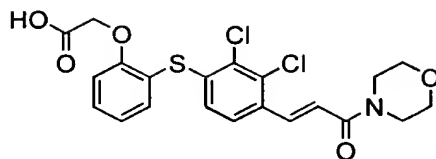
5 temperature for 15 h. Ethyl acetate was added, the mixture was washed with brine, water, and was concentrated. The residual oil was dissolved in THF (3 mL), and was added lithium hydroxide monohydrate (26 mg, 0.62 mmol) in water (1.5 mL). After stirring for 15 hours, the solution was separated by HPLC (Zorbax C-18) to give the

10 title compound (132 mg, 55%).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  1.32 (m, 2H), 1.65 (m, 2H), 1.75 (m, 2H), 1.92 (m, 2H), 2.43 (m, 1H), 2.86 (t,  $J$  = 10.6 Hz, 2H), 3.15 (m, 1H), 3.32 (m, 1H), 3.71 (m, 3H), 3.95 (m, 2H), 6.73 (d,  $J$  = 8.5 Hz, 1H), 6.94 (d,  $J$  = 7.2 Hz, 1H), 7.13 (d,  $J$  = 7.8 Hz, 1H), 7.13 (s, 1H), 7.24 (d,  $J$  = 15.2 Hz, 1H), 7.37 (t,  $J$  = 8.1 Hz, 1H), 7.72 (d,  $J$  = 15.2 Hz, 1H), 7.85 (d,  $J$  = 8.5 Hz, 1H); MS (ESI $^+$ )  $m/z$  535, 537 (M+H) $^+$ . Anal. calcd for  $\text{C}_{26}\text{H}_{28}\text{N}_2\text{Cl}_2\text{SO}_4 \cdot 0.25 \text{ TFA}$ : C, 56.43; H, 5.05; N, 4.97.

15 Found: C, 56.37; H, 5.00; N, 4.91.

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375

Example 413

(2-Glycoxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

5 Diethyl azodicarboxylate (270  $\mu$ L, 1.47 mmol) was added to a suspension of  
 Example 405 (400 mg, 0.95 mmol), triphenylphosphine (386 mg, 1.47 mmol), and  
 THF (2.0 mL). After 16 h, the dark orange solution was diluted with EtOAc (40 mL),  
 washed with 1 N aqueous HCl (1x20 mL), washed with 0.2 N aqueous NaOH (1x20  
 mL), washed with brine (1x20 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated. Flash  
 10 silica gel column chromatography (9:1 hexane:ethyl acetate) provided a mix of  
 desired ester and triphenyl phosphine oxide. The mixture (200 mg) was combined  
 with lithium hydroxide, monohydrate (34 mg, 0.81 mmol), THF (0.5 mL), and  $\text{H}_2\text{O}$   
 (0.5 mL). After 21 h, the cloudy solution was diluted with 0.2 N aqueous NaOH (30  
 mL), washed with  $\text{CH}_2\text{Cl}_2$  (2x15 mL), combined with 1 N aqueous HCl until pH<2,  
 15 and extracted with EtOAc (2x20 mL). The EtOAc extracts were combined, washed  
 with brine (1x20 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated to a white solid (87  
 mg, 47%).  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 300 MHz)  $\delta$  7.80 (d,  $J=7.8$ , 1H), 7.77 (d,  $J=15.3$  Hz,  
 1H), 7.51 (dt,  $J=8.1$  Hz,  $J=2.0$  Hz, 1H), 7.48 (d,  $J=8.1$  Hz, 1H), 7.22 (d,  $J=15.3$  Hz,  
 1H), 7.09 (d,  $J=7.8$  Hz, 1H), 7.08 (dt,  $J=7.1$  Hz,  $J=1.0$  Hz, 1H), 6.71 (d,  $J=8.9$  Hz,  
 20 1H), 4.77 (s, 2H), 3.66 (s, 2H), 3.58 (s, 6H); MS (APCI)  $m/z$  468 ( $\text{M}+\text{H}^+$ ); 466 ( $\text{M}-\text{H}^-$ )

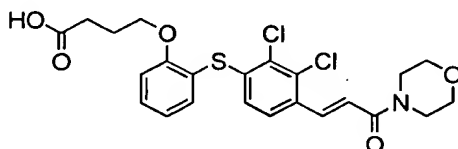
00T000" 562T4560

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143

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, 502 (M+Cl)<sup>+</sup>. Anal. calcd for C<sub>21</sub>H<sub>19</sub>Cl<sub>2</sub>NO<sub>5</sub>S: C, 53.85; H, 4.09; N, 2.99. Found: C, 54.07; H, 4.28; N, 2.69.



5

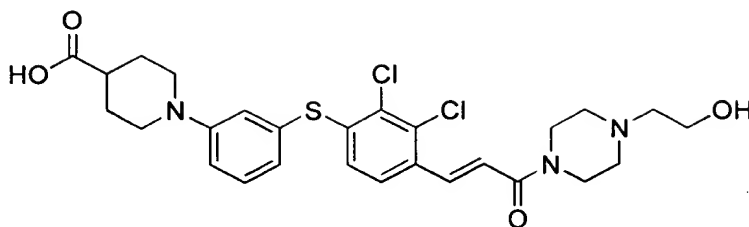
Example 414

(2-(4-Butyroxyl)phenyl)[2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

NOTE: 5627560

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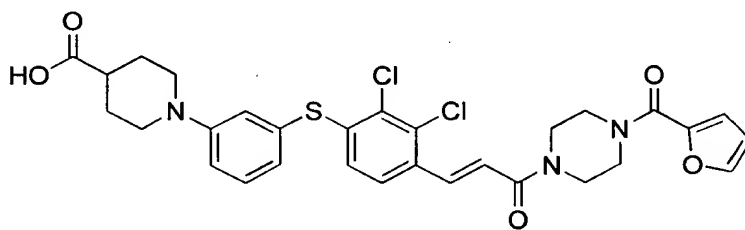
Ethyl 4-bromobutyrate was added to a mixture of Example 405 (300 mg, 0.731 mmol), cesium carbonate (358 mg, 1.10 mmol), and DMF (1.5 mL). After 16 h, the pale milky solution was diluted with EtOAc (30 mL), washed with 1 N aqueous HCl (2x25 mL), washed with brine (1x25 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated to a white solid (326 mg, 85%) as the ethyl ester. The ethyl ester (312 mg, 0.595 mmol), THF (1.5 mL), and H<sub>2</sub>O (1.5 mL) were combined with lithium hydroxide, monohydrate (63 mg, 1.50 mmol). After 18 h, the clear solution was poured into 1 N aqueous HCl (25 mL) and extracted with EtOAc (2x25 mL). The organic layers were combined, dried (MgSO<sub>4</sub>), filtered, and concentrated to a white solid (247 mg, 85%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.79 (d, J=8.5, 1H), 7.77 (d, J=15.6 Hz, 1H), 7.51 (dt, J=7.5 Hz, J=1.7 Hz, 1H), 7.48 (dd, J=7.5 Hz, J=1.0 Hz, 1H), 7.20 (d, J=14.9 Hz, 1H), 7.19 (d, J=9.5 Hz, 1H), 7.06 (t, J=7.5 Hz, 1H), 6.63 (d, J=8.5 Hz, 1H), 4.01 (t, J=6.1 Hz, 2H), 3.65 (s, 2H), 3.58 (s, 6H), 2.10 (t, J=7.4 Hz, 2H), 1.75 (m, 2H); MS (APCI) m/z 496 (M+H)<sup>+</sup>.



### Example 415

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl]phenyl sulfide

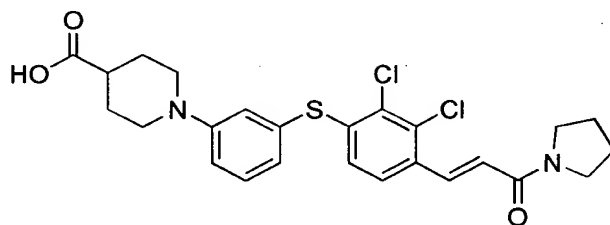
The title compound was prepared by the procedures described in Example 412 substituting 4-hydroxypiperidine with 1-hydroxyethylpiperazine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.70 (m, 2H), 1.94 (m, 2H), 2.98 (m, 2H), 3.05 (m, 2H), 3.18 (m, 2H), 3.54 (m, 2H), 3.65 (m, 3H), 3.78 (m, 2H), 6.77 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 6.8 Hz, 1H), 7.28 (d, J = 14.9 Hz, 1H), 7.29 (m, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.78 (d, J = 15.3 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H); MS (ESI<sup>+</sup>) m/z 564, 566 (M+H)<sup>+</sup>.



### Example 416

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-furoyl)piperazin-1-yl)carbonyl)ethenyl]phenyl sulfide

The title compound was prepared by the procedures described in Example 412 substituting 4-hydroxypiperidine with 1-furoylpiperazine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.64 (m, 2H), 1.91 (m, 2H), 2.43 (m, 1H), 2.87 (m, 2H), 3.70 (m, 10H), 6.43 (m, 1H), 6.72 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 3.3 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.14 (s, 1H), 7.26 (d, J = 15.2 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 15.2 Hz, 1H), 7.86 (m, 2H); MS (ESI<sup>+</sup>) *m/z* 614, 616 (M+H)<sup>+</sup>. Anal. calcd for C<sub>30</sub>H<sub>29</sub>N<sub>3</sub>Cl<sub>2</sub>SO<sub>5</sub> 1.5 TFA: C, 50.45; H, 3.91; N, 5.35. Found: C, 50.53; H, 3.96; N, 5.35.



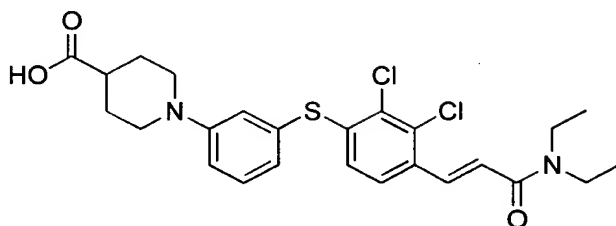
#### Example 417

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((pyrrolidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412 substituting 4-hydroxypiperidine with pyrrolidine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.63 (m, 2H), 1.79 (m, 2H), 1.88 (m, 4H), 2.43 (m, 1H), 2.82 (m, 2H), 3.39 (t, J = 6.7 Hz, 2H), 3.59 (t, J = 6.8 Hz, 2H), 3.68 (m, 2H), 6.71 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 15.3 Hz, 1H), 7.12 (d, J = 6.8 Hz, 1H), 7.13 (s, 1H), 7.35 (t, J = 8.8 Hz, 1H), 7.72 (d, J = 15.3 Hz, 1H), 7.80 (d, J = 8.5 Hz); MS (ESI<sup>+</sup>) *m/z* 505, 507

(M+H)<sup>+</sup>. Anal. calcd for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>Cl<sub>2</sub>SO<sub>3</sub> 0.8 TFA: C, 53.54; H, 4.53; N, 4.69.

Found: C, 53.74; H, 4.40; N, 4.64.



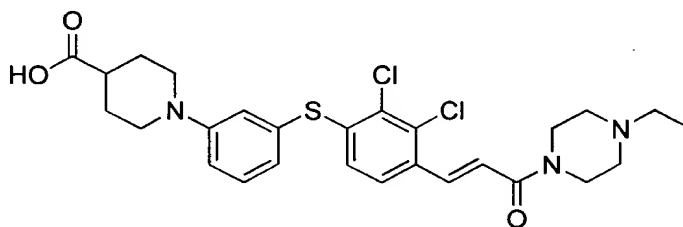
5

### Example 418

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-  
((diethylaminocarbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412 substituting 4-hydroxypiperidine with diethylamine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)

10 δ 1.06(t, J = 6.7 Hz, 3H), 1.11 (t, J = 6.7 Hz, 3H), 1.63 (m, 2H), 1.88 (m, 2H), 2.43  
 (m, 1H), 2.82 (m, 2H), 3.35 (q, J = 6.7 Hz, 2H), 3.47 (q, J = 6.7 Hz, 2H), 3.70 (m,  
 2H), 6.68 (d, J = 8.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.07 (d, J = 15.2 Hz, 1H), 7.12  
 (d, J = 8.6 Hz, 1H), 7.13 (s, 1H), 7.35 (t, J = 8.8 Hz, 1H), 7.75 (d, J = 15.3 Hz, 1H),  
 7.84 (d, J = 8.5 Hz, 1H); MS (ESI<sup>+</sup>) m/z 507 (M+H)<sup>+</sup>. Anal. calcd for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>Cl<sub>2</sub>SO<sub>3</sub>  
 15 0.2 TFA: C, 57.53; H, 5.36; N, 5.28. Found: C, 57.68; H, 5.38; N, 5.33.

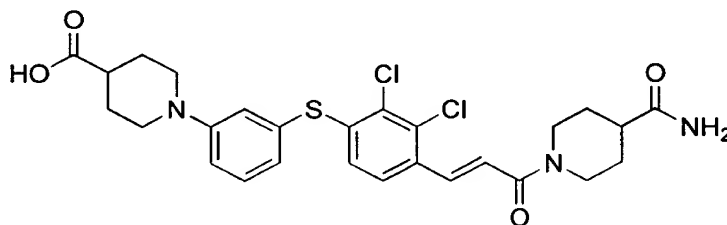


Example 419

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-ethylpiperazin-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412

5 substituting 4-hydroxypiperidine with 1-ethylpiperazine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.22 (t, J = 7.5 Hz, 3H), 1.63 (m, 2H), 1.87 (m, 2H), 2.42 (m, 1H), 2.81 (t, J = 10.5 Hz, 2H), 3.00 (m, 2H), 3.15 (m, 2H), 3.40 (m, 1H), 3.51 (m, 2H), 3.67 (m, 2H), 4.50 (m, 2H), 6.73 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 7.11 (m, 2H), 7.28 (d, J = 15.2 Hz, 1H), 7.36 (m, 1H), 7.80 (d, J = 15.2 Hz, 1H), 7.86 (d, J = 8.5  
10 Hz); MS (APCI<sup>+</sup>) *m/z* 548, 550 (M+H)<sup>+</sup>. Anal. calcd for C<sub>27</sub>H<sub>31</sub>N<sub>3</sub>Cl<sub>2</sub>SO<sub>3</sub> 2.2 TFA: C, 47.18; H, 4.19; N, 5.26. Found: C, 47.27; H, 4.27; N, 5.30.

Example 420

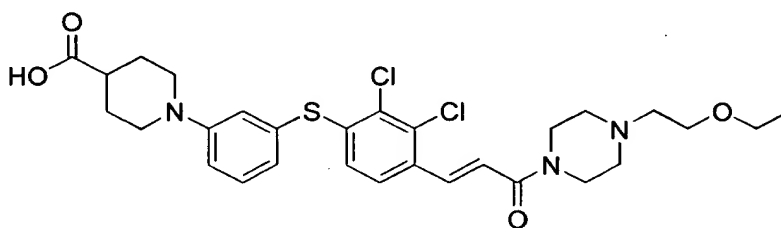
15 [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-(aminocarbonyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412

substituting 4-hydroxypiperidine with isonipecotamide. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.45 (m, 2H), 1.63 (m, 2H), 1.73 (m, 2H), 1.87 (m, 2H), 2.43 (m, 2H), 2.78 (m, 2H), 3.10 (m, 2H), 3.7 (m, 3H), 4.30 (m, 1H), 4.40 (m, 1H), 6.70 (d, J = 8.5 Hz, 1H),  
20 2H), 3.10 (m, 2H), 3.7 (m, 3H), 4.30 (m, 1H), 4.40 (m, 1H), 6.70 (d, J = 8.5 Hz, 1H),

6.78 (s, 1H), 6.92 (d,  $J = 7.5$  Hz, 1H), 7.12 (m, 2H), 7.25 (d,  $J = 15.2$  Hz, 1H), 7.27 (s, 1H), 7.35 (m, 1H), 7.73 (d,  $J = 15.2$  Hz, 1H), 7.86 (d,  $J = 8.6$  Hz, 1H); MS (APCI<sup>+</sup>)  $m/z$  562 (M+H)<sup>+</sup>. Anal. calcd for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>Cl<sub>2</sub>SO<sub>4</sub> 0.2 TFA: C, 56.23; H, 5.03; N, 7.18. Found: C, 56.41; H, 4.96; N, 6.98.

5

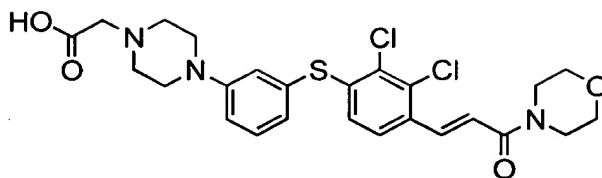


Example 421

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-(2-(ethoxyethyl)piperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

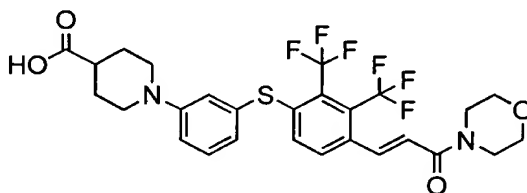
10 The title compound was prepared by the procedures described in Example 412 substituting 4-hydroxypiperidine with 1-(2-ethoxyethyl)piperazine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.15 (t,  $J = 6.8$  Hz, 3H), 1.63 (m, 2H), 1.90 (m, 2H), 2.42 (m, 1H), 2.81 (t,  $J = 10.2$  Hz, 2H), 3.09 (m, 2H), 3.32 (m, 2H), 3.50 (q,  $J = 6.8$  Hz, 2H), 3.51 (m, 2H), 3.68 (m, 4H), 4.45 (m, 2H), 6.73 (d,  $J = 8.6$  Hz, 1H), 6.91 (d,  $J = 7.5$  Hz, 1H), 7.11 (m, 2H), 7.26 (d,  $J = 15.3$  Hz, 1H), 7.36 (m, 1H), 7.80 (d,  $J = 15.2$  Hz, 1H), 7.83 (d,  $J = 8.5$  Hz, 1H); MS (APCI<sup>+</sup>)  $m/z$  592 (M+H)<sup>+</sup>. Anal. calcd for C<sub>29</sub>H<sub>35</sub>N<sub>3</sub>Cl<sub>2</sub>SO<sub>4</sub> 2.5 TFA: C, 46.53; H, 4.31; N, 4.79. Found: C, 46.51; H, 4.31; N, 4.77.

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Example 422

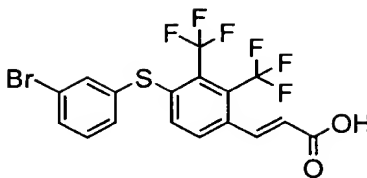
[3-((4-Carboxymethyl)piperazin-1-yl)phenyl] [(2,3-dichloro-4-(E-(4-morpholinyl)carbonyl)ethenyl)phenyl] sulfide

- 5           The title compound (24 mg, 42%) was prepared from Example 393A as described in Example 384D, substituting morpholine with 1-((ethoxycarbonyl)methyl)piperazine, followed by hydrolysis with LiOH as described in Example 340H. <sup>1</sup>H NMR (300 MHz, MeOH-d<sub>4</sub>) δ 3.54 (s, 8H), 3.69 (s, 8H), 4.11 (s, 2H), 6.77 (d, J=8.5 Hz, 1H), 7.06 (d, J=15 Hz, 1H), 7.08 (m, 1H), 7.42 (t, J=7.5
- 10   Hz, 1H), 7.59 (d, J=8.25 Hz, 1H), 7.93 (d, J=15 Hz, 1H); MS (ESI) *m/e* 536, 538 (M+H)<sup>+</sup>.

Example 423

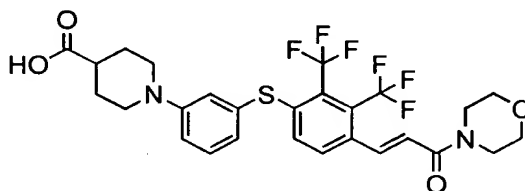
- 15           [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-(4-morpholino)carbonyl)ethenyl]phenyl sulfide

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Example 423A

[3-Bromophenyl] [2,3-bis(trifluoromethyl)-4-(E-(2-carboxy)ethenyl)phenyl]sulfide

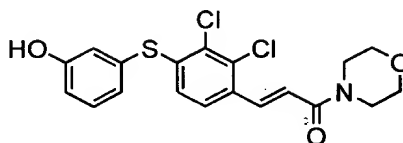
The title compound was prepared from Example 401C using the procedures described in Example 384A, followed by hydrolysis with LiOH as given in Example 340H.

Example 423B

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

The title compound was prepared from Example 423A as described in Example 340G, substituting methyl isonipecotatate with morpholine, followed by amination with ethyl isonipecotatate as described in Example 396, and subsequent hydrolysis according to the procedure of Example 340H. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.5-1.64 (m, 2H), 1.67-1.75 (m, 1H), 1.87-1.96 (m, 1H), 2.49-2.57 (m, 2H), 2.82-2.91 (m, 1H), 2.99-3.06 (m, 1H), 3.46-3.54 (m, 2H), 3.54-3.62 (m, 5H), 3.63-3.72 (m, 3H), 6.87 (d, J=8 Hz, 1H), 7.06-7.13 (m, 2H), 7.16 (d, J=15 Hz, 1H),

7.25-7.36 (m, 2H), 7.66 (dd,  $J_1=15$  Hz,  $J_2=4$  Hz, 1H), 8.00 (d,  $J=8$  Hz, 1H); MS (ESI)  $m/e$  589 (M+H)<sup>+</sup>.



5

Example 424

(3-Hydroxyphenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

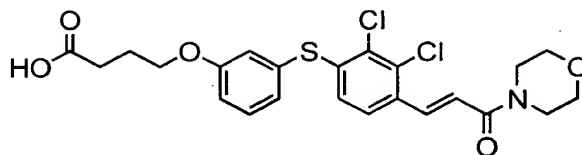
Example 310B was processed as described in Examples 310 and 405, substituting 3-methoxythiophenol for the thiol. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$

10 9.88 (s, 1H), 7.86 (d,  $J=8.8$ , 1H), 7.77 (d,  $J=14.9$  Hz, 1H), 7.33 (dt,  $J=7.4$  Hz,  $J=1.0$  Hz, 1H), 7.24 (d,  $J=14.8$  Hz, 1H), 6.96 (dd,  $J=8.8$  Hz,  $J=1.0$  Hz, 1H), 6.90 (dd,  $J=8.8$  Hz,  $J=1.0$  Hz, 1H), 6.89 (s, 1H), 6.79 (d,  $J=8.5$  Hz, 1H), 3.67 (s, 2H), 3.58 (s, 6H);

MS (APCI)  $m/z$  410 (M+H)<sup>+</sup>, 427 (M+NH<sub>4</sub>)<sup>+</sup>, 408 (M-H)<sup>-</sup>, 446 (M+Cl)<sup>-</sup>. Anal. calcd for C<sub>19</sub>H<sub>17</sub>Cl<sub>2</sub>NO<sub>3</sub>S·0.25 H<sub>2</sub>O: C, 55.01; H, 4.25; N, 3.38. Found: C, 55.15; H, 4.25; N,

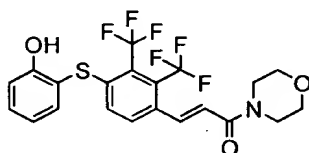
15 3.51.

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Example 425

[3-(4-Butyroxyl)phenyl] [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

5 Example 424 was processed as described in Example 414 to provide the title compound as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.86 (d, *J*=8.8 Hz, 1H), 7.77 (d, *J*=15.3 Hz, 1H), 7.43 (dt, *J*=7.5 Hz, *J*=1.7 Hz, 1H), 7.24 (d, *J*=15.2 Hz, 1H), 7.11 (s, 1H), 6.79 (d, *J*=8.4 Hz, 1H), 6.73 (d, *J*=8.5 Hz, 1H), 4.02 (t, *J*=6.5 Hz, 2H), 3.67 (s, 2H), 3.58 (s, 6H), 2.37 (t, *J*=7.5 Hz, 2H), 1.95 (m, 2H); MS (APCI) *m/z* 410  
10 (M+H<sup>+</sup>), 494 (M-H)<sup>-</sup>, 530 (M+Cl)<sup>-</sup>.

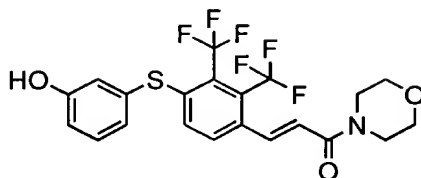
Example 426

(2-Hydroxyphenyl) [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

15 Example 401D was processed as described in Example 405 to provide the title compound as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 10.26 (s, 1H), 7.96 (d, *J*=8.5, 1H), 7.67 (m, 1H), 7.46 (dd, *J*=7.4 Hz, *J*=1.3 Hz, 1H), 7.38 (dt, *J*=7.5 Hz, *J*=1.3 Hz, 1H), 7.16 (d, *J*=15.2 Hz 1H), 7.13 (d, *J*=8.5 Hz, 1H), 7.00 (d, *J*=8.2 Hz,

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1H), 6.90 (t,  $J=7.4$  Hz, 2H), 3.65 (s, 2H), 3.57 (s, 6H). MS (APCI)  $m/z$  478 ( $M+H$ )<sup>+</sup>, 495 ( $M+NH_4$ )<sup>+</sup>; 476 ( $M-H$ )<sup>-</sup>, 512 ( $M+Cl$ )<sup>-</sup>.



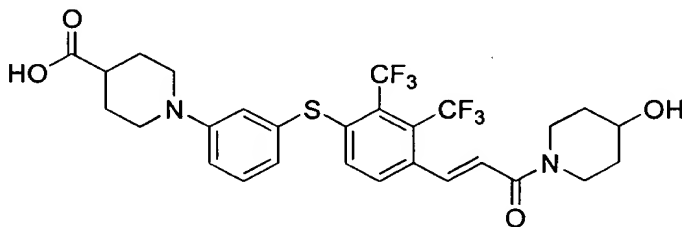
5

Example 427

(3-Hydroxyphenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

Example 401C was processed as described in Example 401D, substituting 3-methoxythiophenol for the thiol, and in Example 405 to provide the title compound as a white solid. <sup>1</sup>H NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  9.86 (s, 1H), 8.02 (d,  $J=8.8$ , 1H), 7.67 (m, 1H), 7.35 (d,  $J=9.5$  Hz, 1H), 7.30 (dt,  $J=7.8$  Hz,  $J=0.7$  Hz, 1H), 7.19 (d,  $J=15.2$  Hz 1H), 6.95 (d,  $J=8.8$  Hz, 1H), 6.88 (d,  $J=7.5$  Hz, 1H), 6.85 (s, 1H), 3.67 (s, 2H), 3.58 (s, 6H). MS (APCI)  $m/z$  478 ( $M+H$ )<sup>+</sup>, 495 ( $M+NH_4$ )<sup>+</sup>, 476 ( $M-H$ )<sup>+</sup>, 512 ( $M+Cl$ )<sup>-</sup>.

15

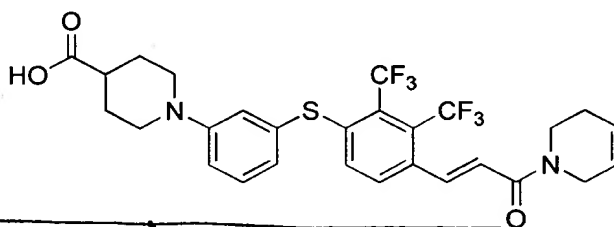
Example 428

Sub  
A  
145

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-ditrifluoromethyl-4-(E-((4-hydroxypiperidin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412 substituting Example 384B with Example 423A. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ

- 5 1.31 (m, 2H), 1.63 (m, 2H), 1.71 (m, 2H), 1.91 (m, 2H), 2.42 (m, 1H), 2.82 (t, J = 10.5 Hz, 2H), 3.16 (m, 1H), 3.31 (m, 1H), 3.70 (m, 3H), 3.93 (m, 2H), 6.88 (d, J = 7.1 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.14 (t, J = 7.1 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.60 (dq, J = 15.2, 4.5 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H); MS (APCI<sup>+</sup>) *m/z* 603 (M+H)<sup>+</sup>. Anal. calcd for C<sub>28</sub>H<sub>28</sub>F<sub>6</sub>N<sub>2</sub>O<sub>4</sub>S 1.15
- 10 TFA: C, 49.60; H, 4.00; N, 3.82. Found: C, 49.65; H, 3.80; N, 3.81.



Example 429

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-ditrifluoromethyl-4-(E-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412 substituting Example 384B with Example 423A, and substituting 4-hydroxypiperidine

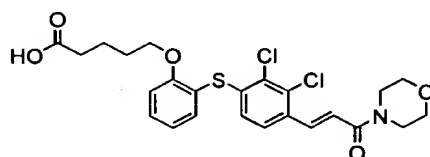
- 15 with 1,2,5,6-tetrahydropyridine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.63 (m, 2H), 1.90 (m, 2H), 2.12 (m, 2H), 2.43 (m, 1H), 2.81 (t, J = 10.5 Hz, 2H), 3.75 (m, 4H),
- 20 4.01 ((s, 1H), 4.15 (s, 1H), 5.73 (m, 1H), 5.84 (m, 1H), 6.87 (d, J = 7.5 Hz, 1H), 7.10

00T E E O " 5 6 2 T H 5 6 0

Sub  
A  
146

(m, 2H), 7.30 (m, 3H), 7.62 (m, 1H), 8.01 (t,  $J = 6.5$  Hz, 1H); MS (APCI<sup>+</sup>)  $m/z$  585

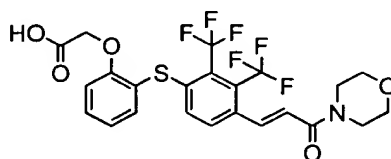
(M+H)<sup>+</sup>. Anal. calcd for C<sub>28</sub>H<sub>26</sub>F<sub>6</sub>N<sub>2</sub>O<sub>3</sub>S 0.1 TFA: C, 56.83; H, 4.41; N, 4.70. Found: C, 56.91; H, 4.44; N, 4.60.



### Example 430

[2-((4-Carboxy)butyloxy)phenyl] [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

Example 405 was processed as described in Example 414, substituting ethyl 5-bromovalerate for the alkyl halide. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  7.79 (d,  $J=8.5$ , 1H), 7.77 (d,  $J=15.3$  Hz, 1H), 7.51 (dt,  $J=8.2$  Hz,  $J=1.7$  Hz, 1H), 7.48 (dd,  $J=7.5$  Hz,  $J=1.7$  Hz, 1H), 7.20 (dd,  $J=7.5$  Hz,  $J=1.7$  Hz, 1H), 7.20 (d,  $J=15.6$  Hz, 1H), 7.05 (dt,  $J=7.5$  Hz,  $J=1.0$  Hz, 1H), 6.63 (d,  $J=8.5$  Hz, 1H), 3.99 (t,  $J=6.1$  Hz, 2H), 3.65 (s, 2H), 3.58 (s, 6H), 2.10 (t,  $J=7.1$  Hz, 2H), 1.56 (m, 2H), 1.39 (m, 2H). MS (APCI)  $m/z$  510 (M+H)<sup>+</sup>. Anal. calcd for C<sub>24</sub>H<sub>25</sub>Cl<sub>2</sub>NO<sub>5</sub>S 0.75 H<sub>2</sub>O: C, 55.02; H, 5.10; N, 2.67. Found: C, 54.72; H, 4.82; N, 2.77.

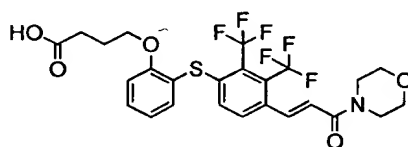


Example 431

(2-Glycoxyphenyl) [ 2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

Example 426 was processed as detailed in Example 414, substituting ethyl

5 bromoacetate for the alkyl bromide. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.94 (d, *J*=8.4, 1H), 7.66 (m, 1H), 7.50 (m, 1H), 7.47 (d, *J*=7.4 Hz, 1H), 7.28 (d, *J*=8.5 Hz, 1H), 7.16 (d, *J*=14.9 Hz, 1H), 7.07 (m, 2H), 4.74 (s, 2H), 3.65 (s, 2H), 3.57 (s, 6H); MS (APCI) *m/z* 536 (M+H)<sup>+</sup>, 553 (M+NH<sub>4</sub>)<sup>+</sup>; 534 (M-H)<sup>+</sup>. Anal. calcd for C<sub>23</sub>H<sub>19</sub>F<sub>6</sub>NO<sub>5</sub>S: C, 51.59; H, 3.58; N, 2.62. Found: C, 51.31; H, 3.63; N, 2.33.

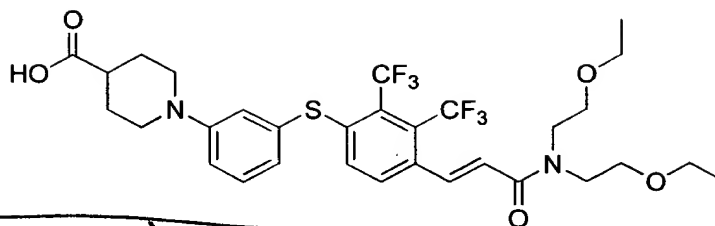
Example 432

(2-(4-Butyroxoy)phenyl)[ 2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

15 Example 426 was processed as described in Example 414 to provide the title compound as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 7.92 (d, *J*=8.5, 1H), 7.65 (m, 1H), 7.59 (d, *J*=7.8 Hz, *J*=1.7 Hz, 1H), 7.50 (t, *J*=8.2 Hz, 1H), 7.15 (d, *J*=8.2 Hz, 1H), 7.12 (d, *J*=15.6 Hz, 1H), 7.09 (d, *J*=8.8 Hz, 1H), 7.07 (t, *J*=7.2 Hz, 1H), 3.92 (t, *J*=6.1 Hz, 2H), 3.65 (s, 2H), 3.57 (s, 6H), 1.99 (t, *J*=7.1 Hz, 2H), 1.63 (m, 2H); MS (APCI) *m/z* 562 (M-H)<sup>+</sup>, 598 (M+Cl)<sup>+</sup>.

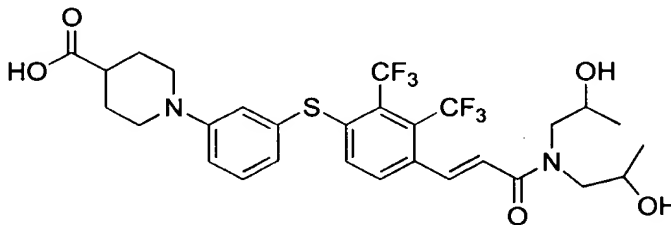
20

390

Example 433

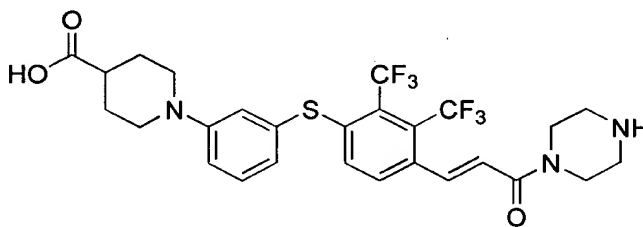
[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-ditrifluoromethyl-4-(E-((bis-(2-ethoxyethyl)amino)carbonyl)ethenyl)phenyl] sulfide

- 5 The title compound was prepared by the procedures described in Example 412 substituting Example 384B with Example 423A, and substituting 4-hydroxypiperidine with bis (2-ethoxyethyl)amine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.99 (t, J = 6.8 Hz, 3H), 1.09 (t, J = 6.8 Hz, 3H), 1.63 (m, 2H), 1.90 (m, 2H), 2.44 (m, 1H), 2.82 (t, J = 10.8 Hz, 2H), 3.40 (m, 4H), 3.50 (m, 6H), 3.68 (m, 4H), 6.88 (d, J = 7.5 Hz, 1H), 7.11 (m, 3H), 7.32 (m, 2H), 7.62 (dq, J = 15.2, 4.5 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H); MS (APCI<sup>+</sup>) m/z 663 (M+H)<sup>+</sup>. Anal. calcd for C<sub>31</sub>H<sub>36</sub>F<sub>6</sub>N<sub>2</sub>O<sub>5</sub>S 0.7 TFA: C, 52.41; H, 4.98; N, 3.77. Found: C, 52.38; H, 4.94; N, 3.68.

Example 434

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis-(trifluoromethyl)-4-(E-((bis-(2-hydroxypropyl)amino)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412 substituting Example 384B with Example 423A, and substituting 4-hydroxypiperidine with diisopropanolamine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.04 (m, 6H), 1.63 (m, 2H), 1.90 (m, 2H), 2.42 (m, 1H), 2.83 (t, J = 10.5 Hz, 2H), 3.04 (m, 1H), 3.26 (m, 1H), 3.45 (m, 2H), 3.67 (m, 2H), 3.75 (m, 1H), 3.90 (m, 1H), 6.90 (d, J = 7.5 Hz, 1H), 7.11 (m, 3H), 7.28 (d, J = 8.5 Hz, 1H), 7.33 (t, J = 8.2 Hz, 1H), 7.63 (m, 1H), 7.95 (dd, J = 8.5, 2.1 Hz, 1H); MS (APCI<sup>+</sup>) *m/z* 635 (M+H)<sup>+</sup>. Anal. calcd for C<sub>29</sub>H<sub>32</sub>F<sub>6</sub>N<sub>2</sub>O<sub>5</sub>S 1.5 TFA: C, 47.71; H, 4.19; N, 3.48. Found: C, 47.52; H, 4.28; N, 3.40.

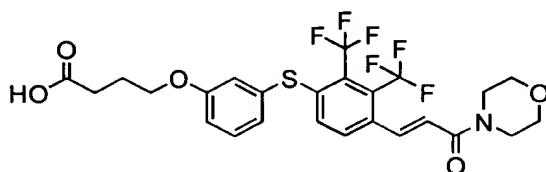


Example 435

[3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis-(trifluoromethyl)-4-(E-((piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared by the procedures described in Example 412 substituting Example 384B with Example 423A, and substituting 4-hydroxypiperidine with 1-(1,2,3,4-tetrahydrofuroyl)piperazine. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.62 (m, 2H), 1.88 (m, 2H), 2.43 (m, 1H), 2.82 (t, J = 10.5 Hz, 2H), 3.15 (br s, 4H), 3.71 (m, 2H), 3.75 (m, 2H), 3.86 (m, 2H), 6.87 (d, J = 7.5 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 15.2 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.35

(d,  $J = 7.8$  Hz, 1H), 7.70 (dt,  $J = 15.2, 4.5$  Hz, 1H), 7.98 (d,  $J = 8.5$  Hz, 1H), 8.85 (br s, 1H); MS (APCI<sup>+</sup>)  $m/z$  588 (M+H)<sup>+</sup>. Anal. calcd for C<sub>27</sub>H<sub>27</sub>F<sub>6</sub>N<sub>3</sub>O<sub>3</sub>S 3.3 TFA: C, 41.87; H, 3.17; N, 4.36. Found: C, 41.78; H, 3.26; N, 4.43.



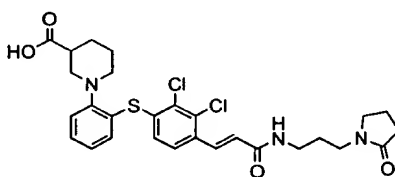
5

### Example 436

(3-(4-Butyroxyl)phenyl)[2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

Example 427 was processed as described in Example 414 to provide the title compound as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz)  $\delta$  8.02 (d,  $J=8.5$ , 1H), 7.65 (m, 1H), 7.40 (t,  $J=7.8$  Hz, 1H), 7.33 (d,  $J=8.8$  Hz, 1H), 7.19 (d,  $J=14.9$  Hz, 1H), 7.09 (m, 3H), 4.02 (t,  $J=6.4$  Hz, 2H), 3.67 (s, 2H), 3.58 (s, 6H), 2.37 (t,  $J=7.1$  Hz, 2H), 1.95 (m, 2H); MS (APCI)  $m/z$  564 (M+H)<sup>+</sup>; 562 (M-H)<sup>-</sup>, 598 (M+Cl)<sup>-</sup>.

15

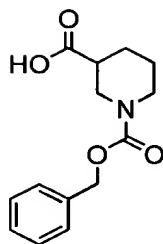


### Example 437

[2-(3-Carboxypiperidin-1-yl)phenyl][2,3-dichloro-4-(E-[(3-(2-pyrrolidinon-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide

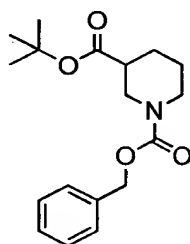
Sub  
A  
148

393

Example 437AN-Benzyloxycarbonyl nipecotic acid

09541795-033100  
Sub 149

To a solution of nipecotic acid (10 g, 63.6 mmol) in 1 N NaOH (2.5 g in 64 ml water, 63.6 mmol) at 0 °C was alternately added benzyloxycarbonyl chloride (10.9 mL, 76.5 mmol) in diethyl ether (50 mL) and 1 N NaOH (5 g in 128 ml water, 127.2 mmol) in five portions. The reaction mixture was stirred at 0 °C for 2 h, and at ambient temperature for 24 h. Then this was made acidic with 10% HCl and the solid formed was filtered and dried (vacuum oven, 45 °C) to obtain the title compound (18.9 g, 113%). MS (ESI)  $m/e$  264 (M+H)<sup>+</sup>.

Example 437Btert-Butyl N-benzyloxycarbonyl nipecotate

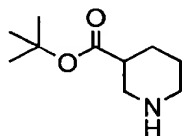
Sub A 150

A solution of Example A (18 g, 62 mmol) in THF (250 mL, 0.25 M) was treated with trichloroacetimidate (28 mL, 155 mmol) and BF<sub>3</sub>·Et<sub>2</sub>O (18 mL, 1 mL/g) at ambient temperature. After 18 h the reaction mixture was quenched with solid

394

Sub A 150

NaHCO<sub>3</sub> followed by water and stirred vigorously. Then the solvent was removed, and partitioned with ethyl acetate (250 mL). The organic layer was separated and washed with brine (3x80 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness under reduced pressure to obtain the crude product. The title compound (19.2 g, 96%) was obtained by flash chromatography on silica gel eluting with 20% acetone:hexane. MS (ESI) *m/e* 320 (M+H)<sup>+</sup>.



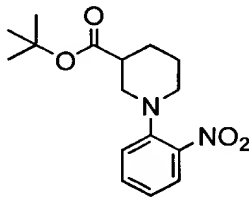
Example 437C

10

tert-Butyl nipecotate

Sub A 151

Example 437B (19 g, 59.5 mmol) was treated with 10% Pd on carbon (2 g, 10 wt %) in ethanol (237 mL, 0.25 M) to obtain the title compound (10.4 g, 94%). MS (ESI) *m/e* 186 (M+H)<sup>+</sup>.



15

Example 437D

2-Nitro-(3-(tert-butyloxycarbonyl)piperidin-1-yl)benzene

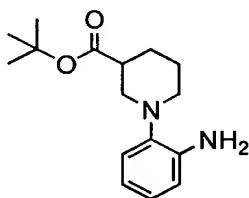
Sub A 152

To a solution of Example 437C (10.4 g, 56.1 mmol) in toluene (112 mL) was added 2-fluoronitrobenzene (6.0 mL, 56 mmol) and CsF (852 mg, 5.6 mmol). The

Sub  
A  
152

reaction mixture was stirred under reflux conditions for 18 h, and allowed to cool to ambient temperature. The mixture was diluted with ethyl acetate (100 ml), washed with 10% HCl (2x50 ml), followed by brine (3x100 ml), then dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated in vacuo to obtain the title compound (16.5 g, 94%). MS (ESI)  $m/e$  307

5 (M+H)<sup>+</sup>.

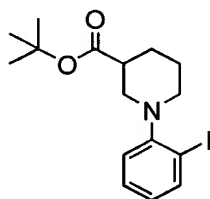


Example 437E

2-Amino-(3-(*tert*-butyloxycarbonyl)piperidin-1-yl)benzene

10 Example 437E (16.4 g, 53.5 mmol) was treated with 10% Pd on carbon (1.65 g, 10 wt %) in ethanol (215 ml, 0.5 M) at ambient temperature for 2 hours. The reaction mixture was filtered through celite and the filtrate was evaporated to dryness under reduced pressure to obtain the title compound (13.45 g, 91%). MS (ESI)  $m/e$  277 (M+H)<sup>+</sup>.

15

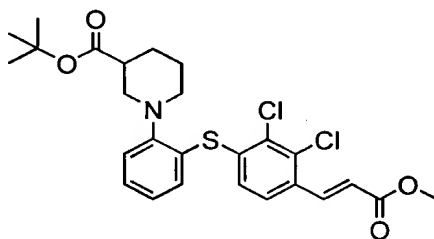


Example 437F

2-Iodo-(3-(*tert*-butyloxycarbonyl)piperidin-1-yl)benzene

Sub  
A153

Example 437E was dissolved in 3 N H<sub>2</sub>SO<sub>4</sub> (195 mL, 0.25 M), cooled to 0 °C and treated with NaNO<sub>2</sub> (3.35 g, 48.6 mmol) in water (20 mL). After 30 minutes at 0 °C potassium iodide (12.01 g, 72.8 mmol) and urea (583 mg, 9.7 mmol) in water (10 mL) were added and stirred for 1 h. The reaction mixture was quenched with 10% NaHCO<sub>3</sub> (50 mL) and partitioned with ethyl acetate (450 mL). The organic layer was separated and washed with 10% NaHCO<sub>3</sub> (2x100 mL), brine (2x100mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness under reduced pressure. The title compound (17.2 g, 91%) was obtained by flash chromatography on silica gel eluting with 10% acetone:hexane. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 1.39 (s, 9H), 6.85 (tt, J<sub>1</sub>=1.5 Hz, J<sub>2</sub>=7.5 Hz, 1H), 7.14 (dd, J<sub>1</sub>=1.5 Hz, J<sub>2</sub>=7.5 Hz, 1H), 7.37 (tt, J<sub>1</sub>=1.5 Hz, J<sub>2</sub>=7.5 Hz, 1H), 7.84 (dd, J<sub>1</sub>=1.5 Hz, J<sub>2</sub>=7.5 Hz, 1H); MS (ESI) *m/e* 388 (M+H)<sup>+</sup>.



Example 437G

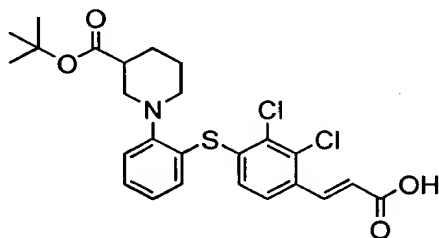
15 [2-(3-tert-Butyloxycarbonyl)piperidin-1-yl]phenyl [2,3-dichloro-4-(E-(2-methoxycarbonyl)ethenyl)phenyl] sulfide

Sub  
A154

Example 437F was converted to the corresponding triisopropylsilyl thiol analogue by the method described for the preparation of Example 340B. Then this intermediate was reacted with Example 340E (2.94 g, 7.75 mmol) at -20 °C as

Sub  
A  
154

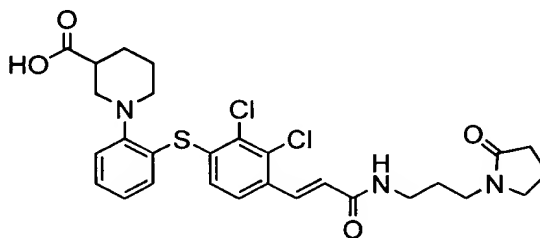
described in Example 340F to obtain the title compound (2.5 g, 63%). MS (ESI)  $m/e$  522, 524 (M+H)<sup>+</sup>.



5 Example 437H

[2-(3-tert-Butyloxycarbonyl)piperidin-1-yl]phenyl] [2,3-dichloro-4-(E-(2-carboxy)ethenyl)phenyl] sulfide

Using the procedure for Example 340H, Example 437H was hydrolyzed to the title compound. MS (ESI)  $m/e$  508, 510 (M+H)<sup>+</sup>.



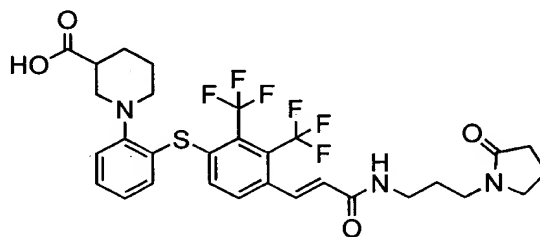
Sub  
A  
155

10 Example 437I

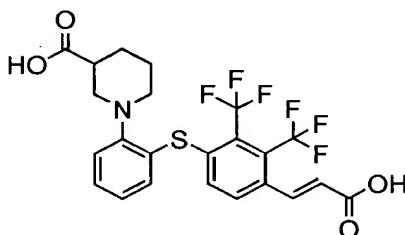
[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-[(3-(2-pyrrolidinon-1-yl)propylaminocarbonyl)ethenyl)phenyl] sulfide

15 The title compound (66 mg) was prepared from Example 437H (90 mg, 0.177 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 3-aminopropyl-2-pyrrolidinone followed by treatment with 20%

TFA in methylene chloride as described in Example 412C.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.27-2.43 (m, 2H), 2.60-2.72 (m, 3H), 2.84 (m, 3H), 2.17-2.30 (m, 3H), 2.62-2.73 (m, 2H), 3.08-3.23 (m, 5H), 3.29-3.38 (m, 3H), 6.62 (d,  $J=15$  Hz, 1H), 6.92 (d,  $J=8.5$  Hz, 1H), 7.12 (t,  $J=7.5$  Hz, 1H), 7.41 (m, 1H), 7.58 (d,  $J=8.75$  Hz, 1H), 7.70 (d,  $J=15$  Hz, 1H), 8.21 (t,  $J=5$  Hz, 1H); MS (ESI)  $m/e$  576, 578 ( $M+H$ ) $^+$ .

Example 438

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-[(3-(2-pyrrolidinon-1-yl)propylaminocarbonyl)ethenyl]phenyl)] sulfide

Example 438A

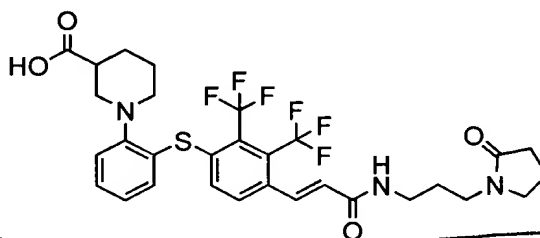
[2-(3-tert-Butyloxycarbonylpiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-(2-carboxy)ethenyl)phenyl] sulfide

The title compound (445 mg, 71%) was prepared from the reaction of

Example 401C (500 mg, 1.08 mmol) with Example 437F, using the procedures

described in Example 437G followed by hydrolysis as described in Example 340G.

MS (ESI)  $m/e$  604 (M+H)

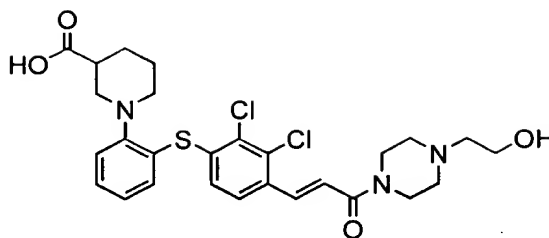


### Example 438B

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-[(3-(2-pyrrolidinon-1-yl)propylaminocarbonyl)ethenyl]phenyl)] sulfide

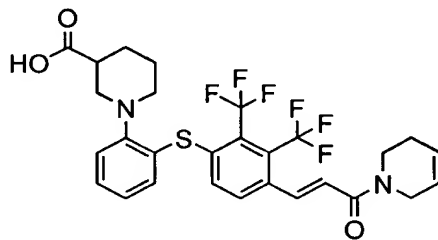
The title compound was prepared from Example 438A (110 mg, 0.191 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 3-aminopropyl-2-pyrrolidinone followed by treatment with 20% TFA in methylene chloride as described in Example 412C.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.11-1.21 (m, 1H), 1.28-1.38 (m, 1H), 1.60-1.70 (m, 3H), 1.79-1.86 (m, 1H), 1.87-1.94 (m, 2H), 2.05-2.12 (m, 1H), 2.00 (t,  $J=7.5$  Hz, 2H), 2.58-2.66 (m, 2H), 2.96-3.01 (m, 1H), 3.11-3.18 (m, 2H), 3.19 (t,  $J=6.25$  Hz, 2H), 3.26 (m, 1H), 3.32 (t,  $J=6.25$  Hz, 2H), 6.46 (d,  $J=15$  Hz, 1H), 7.15 (t,  $J=7.5$  Hz, 1H), 7.33 (m, 2H), 7.43 (m, 1H), 7.62 (m, 1H), 7.75 (d,  $J=7.5$  Hz, 1H), 8.22 (t,  $J=5$  Hz, 1H); MS (ESI)  $m/e$  644 (M+H) $^+$ .

400

Example 439

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-dichloro-4-(E-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

5 The title compound was prepared from Example 437H (90 mg, 0.177 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 1-(2-hydroxyethyl)piperazine followed by treatment with 20% TFA in methylene chloride as described in Example 412C. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 1.31-1.45 (m, 2H), 1.67-1.74 (m, 1H), 1.86-1.92 (m, 1H), 2.24-2.31 (m, 1H), 2.66 (t, J=10 Hz, 1H), 2.73 (t, J=10Hz, 1H), 3.02-3.24 (m, 5H), 3.33-3.38 (m, 1H), 3.52 (m, 3H), 3.75 (t, J=5 Hz, 2H), 4.31-4.60 (m, 3H), 6.90 (d, J=9 Hz, 1H), 7.11 (t, J=7.5 Hz, 1H), 7.21 (d, J=7.5 Hz, 1H), 7.25 (d, J=7.5 Hz, 1H), 7.30 (d, J=15 Hz, 1H), 7.42 (t, J=7.5Hz, 1H), 7.83 (d, J=15 Hz, 1H), 7.85 (d, 9 Hz, 1H); MS (ESI) *m/e* 564, 566 (M+H)<sup>+</sup>.

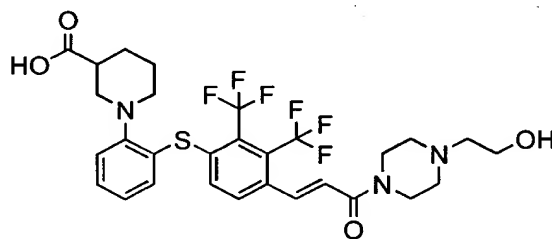
Example 440

00T E E D " 5 6 2 T H 5 6 0

15

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((1,2,5,6-tetrahydropyridin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared from Example 438A (110 mg, 0.191 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 1,2,5,6-tetrahydropyridine followed by treatment with 20% TFA in methylene chloride as described in Example 412C. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 1.19-1.27 (m, 1H), 1.30-1.40 (m, 1H), 1.64-1.70 (m, 1H), 1.80-1.86 (m, 1H), 2.04-2.18 (m, 2H), 2.60 (t, J=10 Hz, 1H), 2.68 (t, J=10 Hz, 1H), 3.03 (br d, J=10 Hz, 1H), 3.23 (br d, J=10 Hz, 1H), 3.60-3.74 (m, 2H), 3.91-4.20 (m, 3H), 5.68-5.74 (m, 1H), 5.80-5.90 (m, 1H), 7.06-7.19 (m, 2H), 7.20-7.28 (m, 2H), 7.36 (m, 1H), 7.44 (t, J=7.5 Hz, 1H), 7.62-7.71 (m, 1H), 7.94-8.04 (m, 1H); MS (ESI) m/e 585 (M+H)<sup>+</sup>.

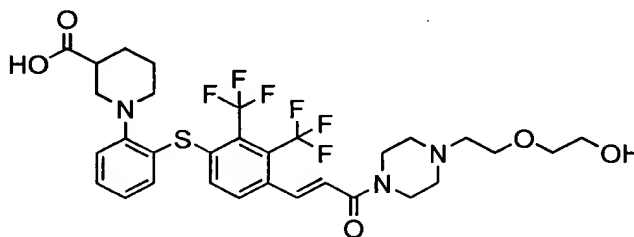


Example 441

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-(2-hydroxyethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared from Example 438A (110 mg, 0.191 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 1-(2-hydroxyethyl)piperazine followed by treatment with 20% TFA in methylene

chloride as described in Example 412C.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.17-1.27 (m, 1H), 1.17-1.27 (m, 1H), 1.31-1.41 (m, 1H), 1.64-1.71 (m, 1H), 1.80-1.88 (m, 1H), 2.07-2.15 (m, 1H), 2.61 (t,  $J=10$  Hz, 1H), 2.09 (t,  $J=10$  Hz, 1H), 2.91-3.13 (m, 3H), 3.18-3.28 (m, 3H), 3.44-3.58 (m, 3H), 3.75 (t,  $J=5$  Hz, 2H), 4.29-4.58 (m, 3H), 7.15 (d,  $J=7.5$  Hz, 1H), 7.19 (d,  $J=10$  Hz, 1H), 7.28 (d,  $J=7.5$  Hz, 2H), 7.37 (d,  $J=7.5$  Hz, 1H), 7.45 (t,  $J=7.5$  Hz, 1H), 7.69-7.77 (m, 1H), 7.98 (d,  $J=7.5$  Hz, 1H), 9.77 (br s, 1H); MS (ESI)  $m/e$  632 ( $M+H$ ) $^+$ .

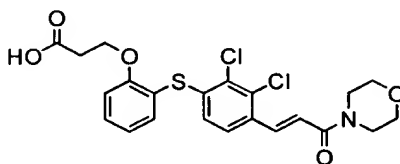


Example 442

[2-(3-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-(2-(hydroxyethoxy)ethyl)piperazin-1-yl)carbonyl)ethenyl)phenyl] sulfide

The title compound was prepared from Example 438A (110 mg, 0.191 mmol), using the procedures described in Example 340G substituting methyl isonipecotate with 1-[2-(2-hydroxyethoxy)ethyl]piperazine followed by treatment with 20% TFA in methylene chloride as described in Example 412C.  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.17-1.27 (m, 1H), 1.31-1.40 (m, 1H), 1.64-1.70 (m, 1H), 1.80-1.86 (m, 1H), 2.08-2.16 (m, 1H), 2.61 (t,  $J=10$  Hz, 1H), 2.68 (t,  $J=10$  Hz, 1H), 3.03 (br d  $J=10$  Hz, 1H), 3.06-3.18 (m, 2H), 3.25 (br d,  $J=10$  Hz, 1H), 3.33 (m, 2H), 3.42-3.51 (m, 2H), 3.53-

3.60 (m, 2H), 3.70-3.80 (m, 5H), 4.32-4.56 (m, 3H), 7.13-7.21 (m, 2H), 7.27 (d,  $J=9$  Hz, 2H), 7.35 (d,  $J=7.5$  Hz, 1H), 7.44 (t,  $J=7.5$  Hz, 1H), 7.68-7.77 (m, 1H), 7.44-8.01 (m, 1H), 9.81 (br s, 1H); MS (ESI)  $m/e$  676 ( $M+H$ )<sup>+</sup>.



### Example 443

(3-(3-Propioxy)phenyl) [2,3-dichloro-4-(E-((4-morpholino)carbonyl)ethenyl)phenyl]sulfide

5  $\beta$ -Propiolactone (50  $\mu$ L, 0.75 mmol) was added to a mixture of Example 405  
 10 (308 mg, 0.75 mmol), potassium *tert*-butoxide (750 mL, 1 M in THF), and THF (1.0 mL). After 18 h, the reaction was diluted with EtOAc, washed with 1 M aqueous HCl, washed with brine, dried ( $MgSO_4$ ), filtered, and concentrated. Purification by preparative HPLC provided the title compound (72 mg, 20%) as a white solid. <sup>1</sup>H  
 15 NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  7.80 (d,  $J=8.4$  Hz, 1H), 7.78 (d,  $J=15.8$  Hz, 1H), 7.52 (dt,  $J=8.8$  Hz,  $J=1.7$  Hz, 1H), 7.46 (dd,  $J=7.8$  Hz,  $J=17$  Hz, 1H), 7.23 (d,  $J=9.1$  Hz, 1H), 7.22 (d,  $J=15.3$  Hz, 1H), 7.08 (t,  $J=7.4$  Hz, 1H), 6.58 (d,  $J=8.5$  Hz, 1H), 4.22 (m, 2H), 4.05 (m, 2H), 3.66 (s, 2H), 3.58 (s, 6H); MS (APCI)  $m/z$  482 ( $M+H$ )<sup>+</sup>; 480 ( $M-H$ )<sup>-</sup>.

Compounds that antagonize the interaction between ICAM-1 and LFA-1 can be identified, and their activities quantitated, using both biochemical and cell-based adhesion assays. A primary biochemical assay measures the ability of the compound

5 in question to block the interaction between the integrin LFA-1 and its adhesion partner ICAM-1, as described below:

#### ICAM-1 / LFA-1 Biochemical Interaction Assay

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In the biochemical assay, 100  $\mu$ L of anti-LFA-1 antibody (ICOS Corporation)

10 at a concentration of 5  $\mu$ g/ml in Dulbecco's phosphate-buffered saline (D-PBS) is used to coat wells of a 96-well microtiter plate overnight at 4°C. The wells are then washed twice with wash buffer (D-PBS w/o  $\text{Ca}^{++}$  or  $\text{Mg}^{++}$ , 0.05% Tween 20) and blocked by addition of 200  $\mu$ L of D-PBS, 5% fish skin gelatin. Recombinant LFA-1 (100  $\mu$ L of 0.7  $\mu$ g/ml, ICOS Corporation) in D-PBS is then added to each well.

15 Incubation continues for 1 hour at room temperature and the wells are washed twice with wash buffer. Serial dilutions of compounds being assayed as ICAM-1/LFA-1 antagonists, prepared as 10 mM stock solutions in dimethyl sulfoxide (DMSO), are diluted in D-PBS, 2mM  $\text{MgCl}_2$ , 1% fish skin gelatin and 50  $\mu$ L of each dilution added to duplicate wells. This is followed by addition of 50  $\mu$ L of 0.8  $\mu$ g/ml biotinylated

20 recombinant ICAM-1/Ig (ICOS Corporation) to the wells and the plates are incubated at room temperature for 1 hour. The wells are then washed twice with wash buffer and 100  $\mu$ L of Europium-labeled Streptavidin (Wallac Oy) diluted 1:100 in Delfia assay

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buffer (Wallac Oy) are added to the wells. Incubation proceeds for 1 hour at room temperature. The wells are washed eight times with wash buffer and 100  $\mu$ L of enhancement solution (Wallac Oy, cat. No. 1244-105) are added to each well. Incubation proceeds for 5 minutes with constant mixing. Time-resolved fluorimetry measurements are made using the Victor 1420 Multilabel Counter (Wallac Oy) and the percent inhibition of each candidate compound is calculated using the following equation:

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$$\% \text{ inhibition} = 100 \times \left\{ 1 - \frac{\text{average OD w/ compound minus background}}{\text{average OD w/o compound minus background}} \right\}$$

where "background" refers to wells that are not coated with anti-LFA-1 antibody.

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Compounds of the present invention exhibit inhibitory activity in the above assay. % inhibition at 4  $\mu$ M was demonstrated.

- Biologically relevant activity of the compounds in this invention is
- 5 confirmed using a cell-based adhesion assay, which measures their ability to block the adherence of JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface) to immobilized ICAM-1, as follows:

ICAM-1 / JY-8 cell adhesion assay

- 10 For measurement of inhibitory activity in the cell-based adhesion assay, 96-well microtiter plates are coated with 70  $\mu$ L of recombinant ICAM-1/Ig (ICOS Corporation) at a concentration of 5  $\mu$ g/mL in D-PBS w/o  $\text{Ca}^{++}$  or  $\text{Mg}^{++}$  overnight at 4°C. The wells are then washed twice with D-PBS and blocked by addition of 200  $\mu$ L of D-PBS, 5% fish skin gelatin by incubation for 1 hour at room temperature.
- 15 Fluorescent tagged JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface; 50  $\mu$ L at  $2 \times 10^6$  cells/ml in RPMI 1640/1% fetal bovine serum) are added to the wells. For fluorescent labeling of JY-8 cells,  $5 \times 10^6$  cells washed once in RPMI 1640 are resuspended in 1 mL of RPMI 1640 containing 2  $\mu$ M Calcein AM (MolecularProbes), are incubated at 37°C for 30 minutes and
- 20 washed once with RPMI-1640/ 1% fetal bovine serum. Dilutions of compounds to be assayed for ICAM-1/LFA-1 antagonistic activity are prepared in RPMI-1640/ 1% fetal bovine serum from 10mM stock solutions in DMSO and 50  $\mu$ L are added to

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duplicate wells. Microtiter plates are incubated for 45 minutes at room temperature and the wells are washed gently once with RPMI-1640/ 1% fetal bovine serum.

Fluorescent intensity is measured in a fluorescent plate reader with an excitation wavelength at 485 nM and an emission wavelength at 530 nM. The percent

- 5 inhibition of a candidate compound at a given concentration is calculated using the following equation:
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$$\% \text{ inhibition} = 100 \times \left\{ 1 - \frac{\text{average OD w/ compound}}{\text{average OD w/o compound}} \right\}$$

- 10 and these concentration/inhibition data are used to generate dose response curves, from which IC<sub>50</sub> values are derived.

Compounds of the present invention exhibit blocking activity in the above assay. Inhibition at 4 μM was demonstrated.

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Compounds of the present invention have been demonstrated to act via interaction with the integrin LFA-1, specifically by binding to the interaction domain (I-domain), which is known to be critical for the adhesion of LFA-1 to a variety of cell adhesion molecules. As such, it is expected that these compounds  
20 should block the interaction of LFA-1 with other CAM's. This has in fact been demonstrated for the case of ICAM-3. Compounds of the present invention may be

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evaluated for their ability to block the adhesion of JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface) to immobilized ICAM-3, as follows:

#### 5 ICAM-3 / JY-8 cell adhesion assay

For measurement of inhibitory activity in the cell-based adhesion assay, 96-well microtiter plates are coated with 50  $\mu$ L of recombinant ICAM-3/Ig (ICOS Corporation) at a concentration of 10  $\mu$ g/mL in D-PBS w/o  $\text{Ca}^{++}$  or  $\text{Mg}^{++}$  overnight at 4°C. The wells are then washed twice with D-PBS, blocked by addition of 100  $\mu$ L of D-PBS, 1% bovine serum albumin (BSA) by incubation for 1 hour at room temperature, and washed once with RPMI-1640 / 5% heat-inactivated fetal bovine serum (adhesion buffer). Dilutions of compounds to be assayed for ICAM-3/LFA-1 antagonistic activity are prepared in adhesion buffer from 10 mM stock solutions in DMSO and 100  $\mu$ L are added to duplicate wells. JY-8 cells (a human EBV-transformed B cell line expressing LFA-1 on its surface; 100  $\mu$ L at  $0.75 \times 10^6$  cells/ml in adhesion buffer) are then added to the wells. Microtiter plates are incubated for 30 minutes at room temperature; the adherent cells are then fixed with 50  $\mu$ L of 14% glutaraldehyde/D-PBS and incubated for an additional 90 minutes. The wells are washed gently with  $\text{dH}_2\text{O}$ ; 50  $\mu$ L of  $\text{dH}_2\text{O}$  is added, followed by 50  $\mu$ L of 1% crystal violet. After 5 minutes the plates are washed 3X with  $\text{dH}_2\text{O}$ ; 75  $\mu$ L of  $\text{dH}_2\text{O}$  and 225  $\mu$ L of 95% EtOH are added to each well to extract the crystal violet from the cells. Absorbance is measured at 570 nm in an ELISA plate reader.

The percent inhibition of a candidate compound is calculated using the following equation:

$$\% \text{ inhibition} = 100 \times \left\{ 1 - \frac{\text{average OD w/ compound}}{\text{average OD w/o compound}} \right\}$$

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Compounds of the present invention exhibit blocking activity in the above assay. 100 % inhibition at 0.6  $\mu$ M was demonstrated.

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**Additional JY-8 (ICAM/LFA-1) Cell Adhesion Assay Protocol****Reagents**

- ICAM-1/Ig, ICOS
- 5    • D-PBS, Dulbecco's w/o Ca & Mg
- D-PBS, Dulbecco's w/ Ca & Mg
- Blocking Solution: 1% non-fat dried milk in PBS w/o Ca & Mg
- RPMI 1640 media
- RPMI 1640 media with 1%FBS (RPMI-1%FBS)
- 10    • RPMI 1640 media with 50%FBS (RPMI-50%FBS)
- 1 mM Calcein AM, Molecular Probes, cat. C-1430 or C-3099
- DMSO
- JY-8 cells

**15    Procedure**

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1. Coat plate (70ul/well) with 5ug/ml in D-PBS w/ Ca & Mg of ICAM-1/Ig. Cover and incubate overnight at 4°C.
  2. Make compound and control dilutions using RPMI-1%FBS and RPMI-50%FBS as the diluents.
  - 20    3. Decant ICAM-1/Ig coated plate(s), and wash 3X with D-PBS w/o Ca & Mg.
  4. Block entire plate(s) with 150ul/well of Blocking solution. Cover and incubate for approximately 1 hour at room temperature.
  5. Count the number of viable JY-8 cells using standard methodology. Need approximately 10-15 x10E6 cells per 96mw tray.

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6. Wash cells 1X in RPMI 1640 media without serum - centrifuging for 5 minutes at approximately 1400rpms. Remove supernate and resuspend cell pellet to  $5 \times 10^6$  cells per ml in RPMI 1640 media without serum.
  7. Add 2ul of 1mM Calcein AM for every 1ml of cell suspension. Mix. Incubate for 30-60 minutes at 37 degrees C in a CO2 incubator (keeping cap of centrifuge tube loose for gas exchange).
  8. Add approximately 10mls of RPMI-1%FBS, aliquot into two equal pools and centrifuge for 5 minutes at 1400rpms.
  9. Remove supernate from each pool and resuspend each cell pellet to  $2 \times 10^6$  cell per ml with RPMI-1%FBS or RPMI-50%FBS.
  10. Decant blocked 96mw plate(s) and wash 3X with D-PBS w/o Ca & Mg.
  11. Add 50ul/well of each compound dilution or control. Add 50ul of Calcein labeled JY-8 cells to all wells. Centrifuge plate(s) briefly (2-5 seconds) at 100-150rpms. Cover and incubate for 30-60 minutes at 37 degrees C.
  12. Gently wash wells 1X with approximately 150ul per well of PBS w/Ca & Mg. Remove all liquid from wells.

13. Read absorbence using reader with an excitation of 485/20 and an emission of 530/25.

14. Calculate % inhibition using the following equation:

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$$\% \text{ inhibition} = 100 \times \left\{ 1 - \frac{\text{average OD w/ compound}}{\text{average OD w/o compound}} \right\}$$

The ability of the compounds of this invention to treat arthritis can be

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demonstrated in a murine collagen-induced arthritis model according to the method of Kakimoto, et al., *Cell Immunol* 142: 326-337, 1992, in a rat collagen-induced arthritis model according to the method of Knoerzer, et al., *Toxicol Pathol* 25:13-19, 1997, in a rat adjuvant arthritis model according to the method of Halloran, et al., *Arthritis Rheum* 39: 810-819, 1996, in a rat streptococcal cell wall-induced arthritis model according to the method of Schimmer, et al., *J Immunol* 160: 1466-1477, 1998, or in a SCID-mouse human rheumatoid arthritis model according to the method of Oppenheimer-Marks et al., *J Clin Invest* 101: 1261-1272, 1998.

The ability of the compounds of this invention to treat Lyme arthritis can be

15 demonstrated according to the method of Gross et al., *Science* 281, 703-706, 1998.

The ability of compounds of this invention to treat asthma can be

demonstrated in a murine allergic asthma model according to the method of Wegner et al., *Science* 247:456-459, 1990, or in a murine non-allergic asthma model according to the method of Bloemen et al., *Am J Respir Crit Care Med* 153:521-529, 1996.

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The ability of compounds of this invention to treat inflammatory lung injury can be demonstrated in a murine oxygen-induced lung injury model according to the method of Wegner et al., *Lung* 170:267-279, 1992, in a murine immune complex-induced lung injury model according to the method of Mulligan et al., *J Immunol* 154:1350-1363, 1995, or in a murine acid-induced lung injury model according to the method of Nagase, et al., *Am J Respir Crit Care Med* 154:504-510, 1996.

The ability of compounds of this invention to treat inflammatory bowel disease can be demonstrated in a rabbit chemical-induced colitis model according to the method of Bennet et al., *J Pharmacol Exp Ther* 280:988-1000, 1997.

The ability of compounds of this invention to treat autoimmune diabetes can be demonstrated in an NOD mouse model according to the method of Hasagawa et al., *Int Immunol* 6:831-838, 1994, or in a murine streptozotocin-induced diabetes model according to the method of Herrold et al., *Cell Immunol* 157:489-500, 1994.

The ability of compounds of this invention to treat inflammatory liver injury can be demonstrated in a murine liver injury model according to the method of Tanaka et al., *J Immunol* 151:5088-5095, 1993.

The ability of compounds of this invention to treat inflammatory glomerular injury can be demonstrated in a rat nephrotoxic serum nephritis model according to the method of Kawasaki, et al., *J Immunol* 150:1074-1083, 1993.

The ability of compounds of this invention to treat radiation-induced enteritis can be demonstrated in a rat abdominal irradiation model according to the method of Panes et al., *Gastroenterology* 108:1761-1769, 1995.

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The ability of compounds of this invention to treat radiation pneumonitis can be demonstrated in a murine pulmonary irradiation model according to the method of Hallahan et al., *Proc Natl Acad Sci U S A* 94:6432-6437, 1997.

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The ability of compounds of this invention to treat reperfusion injury can be demonstrated in the isolated rat heart according to the method of Tamiya et al., *Immunopharmacology* 29(1): 53-63, 1995, or in the anesthetized dog according to the model of Hartman et al., *Cardiovasc Res* 30(1): 47-54, 1995.

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The ability of compounds of this invention to treat pulmonary reperfusion injury can be demonstrated in a rat lung allograft reperfusion injury model according to the method of DeMeester et al., *Transplantation* 62(10): 1477-1485, 1996, or in a rabbit pulmonary edema model according to the method of Horgan et al., *Am J Physiol* 261(5): H1578-H1584, 1991.

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The ability of compounds of this invention to treat stroke can be demonstrated in a rabbit cerebral embolism stroke model according the method of Bowes et al., *Exp Neurol* 119(2): 215-219, 1993, in a rat middle cerebral artery ischemia-reperfusion

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model according to the method of Chopp et al., *Stroke* 25(4): 869-875, 1994, or in a rabbit reversible spinal cord ischemia model according to the method of Clark et al., *Neurosurg* 75(4): 623-627, 1991.

- 5           The ability of compounds of this invention to treat peripheral artery occlusion can be demonstrated in a rat skeletal muscle ischemia / reperfusion model according to the method of Gute et al., *Mol Cell Biochem* 179: 169-187, 1998.

- The ability of compounds of this invention to treat graft rejection can be
- 10   demonstrated in a murine cardiac allograft rejection model according to the method of Isobe et al., *Science* 255: 1125-1127, 1992, in a murine thyroid gland kidney capsule model according to the method of Talento et al., *Transplantation* 55: 418-422, 1993, in a cynomolgus monkey renal allograft model according to the method of Cosimi et al., *J Immunol* 144: 4604-4612, 1990, in a rat nerve allograft model according to the
- 15   method of Nakao et al., *Muscle Nerve* 18: 93-102, 1995, in a murine skin allograft model according to the method of Gorczynski and Wojcik, *J Immunol* 152 : 2011-2019, 1994, in a murine corneal allograft model according to the method of He et al., *Ophthalmol Vis Sci* 35: 3218-3225, 1994, or in a xenogeneic pancreatic islet cell transplantation model according to the method of Zeng et al., *Transplantation* 58:681-
- 20   689, 1994.

The ability of compounds of this invention to treat graft-vs.-host disease (GVHD) can be demonstrated in a murine lethal GVHD model according to the method of Harning et al., *Transplantation* 52:842-845, 1991.

- The ability of compounds of this invention to treat cancers can be
- 5 demonstrated in a human lymphoma metastasis model (in mice) according to the method of Aoudjit et al., *J Immunol* 161:2333-2338, 1998.

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